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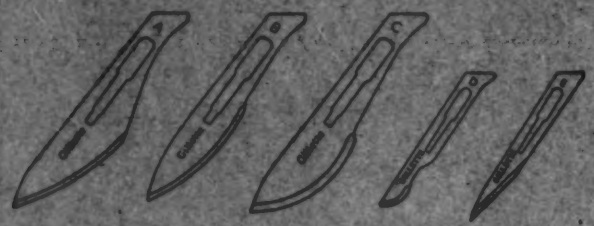

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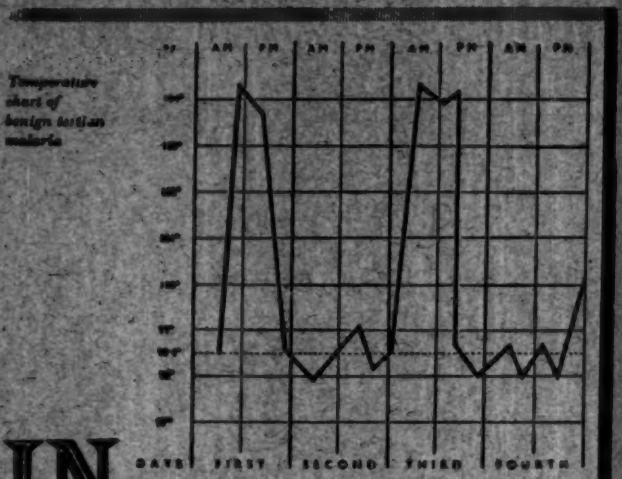

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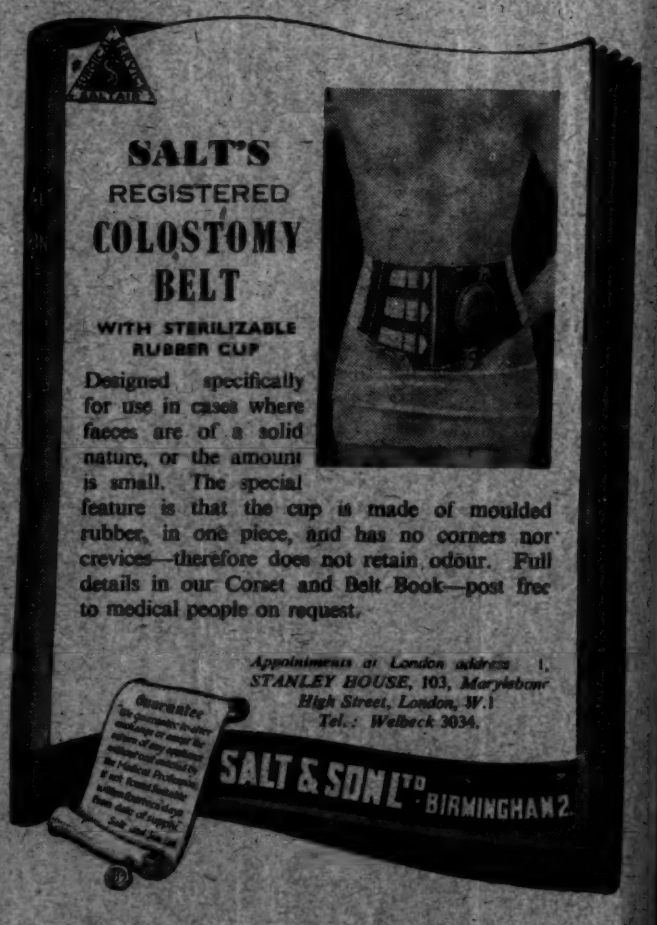

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 24 1950

AMINOPTERIN IN THE TREATMENT OF ACUTE LEUKAEMIA

BY

J. V. DACIE, M.B., M.R.C.P. E. DRESNER, M.B.
D. L. MOLLIN, M.B., B.Sc. AND J. C. WHITE, M.B.

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[WITH PHOTOGRAVURE PLATE]

Since the synthesis of pteroylglutamic acid (folic acid) by Angier *et al.* (1945), several analogues having either a similar or a biologically antagonistic activity have been prepared (Smith *et al.*, 1948). Of the antagonists, the most potent is 4-aminopteroylglutamic acid ("aminopterin"), produced by the substitution of an NH_2 group for the OH group in the 4 position of the pteridine ring of the folic acid molecule (Seeger *et al.*, 1947).

The first report of the use of folic acid antagonists in acute leukaemia was that of Meyer (1948), who obtained temporary clinical and haematological improvement in four of five cases treated with pteroylaspartic acid and methylpteroic acid. Subsequently, Farber *et al.* (1948) reported important remissions in 10 out of 16 children with acute leukaemia treated with aminopterin. The drug seemed to have a pronounced effect on leukaemic bone marrow, causing a decrease or disappearance of leukaemic cells and a reversion to normal of the peripheral white cell count, whether initially high or leucopenic. Immature cells in the blood decreased in numbers or disappeared, and in favourable cases there was an increase in the proportion of mature leucocytes and a rise in red cells, platelets, and haemoglobin. Visceral deposits were affected as well, and when present, enlargement of the spleen, liver, and lymph nodes diminished.

The remission rate in the above series was far beyond the rate of spontaneous remissions to be expected in acute leukaemia. Similar but less striking results have been reported after the use of aminopterin and other antagonists by Pierce and Alt (1948), Stickney *et al.* (1948), Dameshek (1948), Meyer *et al.* (1949), and Wolman *et al.* (1949). In a more recent report, Farber (1949), using aminopterin, "amethopterin" (4-amino-N10-methylpteroylglutamic acid), and "amino-an-fol" (4-aminopteroylaspartic acid), has reported a 50% remission rate in 60 children with acute leukaemia treated for three months or more, including remissions of 16 and 23 months. All authors stress the temporary nature of the remissions induced and the unpredictability of action and the narrow therapeutic margin of the drugs used.

This study is based on 14 cases of acute and subacute leukaemia in adults and children treated with aminopterin. One patient died within 36 hours of admission and has been excluded from the series. The results of treatment in 13 cases are presented.

Case 1. Acute Monocytic Leukaemia

A male school-teacher aged 45 first noticed undue dyspnoea on exertion and sore throat whilst mountaineering on August 18, 1948. These symptoms became worse, and a week later he developed a purple rash on the abdomen, night sweats, and increasing general weakness. By September 15 the rash had become generalized and splinter haemorrhages had appeared beneath the nails. He was admitted to another hospital, where his condition rapidly deteriorated, and on September 20 he was transferred to Hammersmith Hospital as a case of acute leukaemia.

On examination he was seen to be a well-built man, but wasted and weak, with a temperature of 103° F. (39.4° C.). A purplish maculo-papular rash involved the face, trunk, and extremities, with some oedema of the underlying tissues. In addition there were purpuric spots on the legs, which were confluent in places. The gums were spongy but not bleeding, and he had stomatitis and a purulent tonsillitis. All superficial lymph nodes were enlarged. No abnormalities were found in the lungs or in the cardiovascular or central nervous systems. The liver was enlarged 2½ in. (6.3 cm.), and the spleen ½ in. (1.25 cm.) below the costal margins. The urine contained albumin and excess urobilinogen. A radiograph of the chest was normal. A blood count showed: red cells, 2,600,000 per c.mm.; haemoglobin, 8.6 g. per 100 ml.; platelets, 230,000 per c.mm.; white cells, 6,000 per c.mm. (polymorphs 10%, lymphocytes 15%, monocytes 75%).

Marrow Biopsy.—Sternal puncture. About 60% of the marrow cells were large atypical mononuclears of varying maturity, the most primitive resembling reticulum cells. Slightly less primitive cells had large nuclei with several nucleoli and a moderate amount of basophilic cytoplasm. The most mature cells resembled monocytes. Less than 1% of the total nucleated cells were erythroblasts (Plate, Fig. 1).

Skin biopsy of a cutaneous papule showed the dermis to be infiltrated with mononuclear cells, the appearance being that of leukaemic infiltration.

Treatment and Progress

Parenteral penicillin was given throughout the illness. A total of 20 mg. of aminopterin in daily doses of 1 mg. was given intramuscularly from September 24 to October 16, and several blood transfusions were found necessary. The result of treatment was that the throat condition rapidly resolved, the temperature fell, and the patient's general condition improved remarkably. He regained his appetite, and his weight rose. The cutaneous infiltrations began to disappear soon after treatment started and had faded before it was completed. The lymph nodes, liver, and spleen were still enlarged, but had diminished considerably in size. Purpura had vanished.

Treatment was complicated by the development of a large haematoma in the right thigh at the site of a penicillin injection; this broke down and formed an indolent ulcer, but by the end of October it had healed and he was able to get up feeling reasonably well. Puncture of a vertebral spine on October 16 showed that the marrow was much less leukaemic. Only 5% of the cells were reticulum cells or monocytes and 20% were erythroblasts. Erythropoiesis was predominantly normoblastic, but a few intermediate megaloblasts were present (Plate, Fig. 2). This improvement in the marrow was reflected in the peripheral blood. The proportion of mature polymorphs rose to 50–60% and only 2–5% of the cells were abnormal monocytes. The total white cells rose to normal levels and platelets increased to 350,000 per c.mm. (Fig. A).

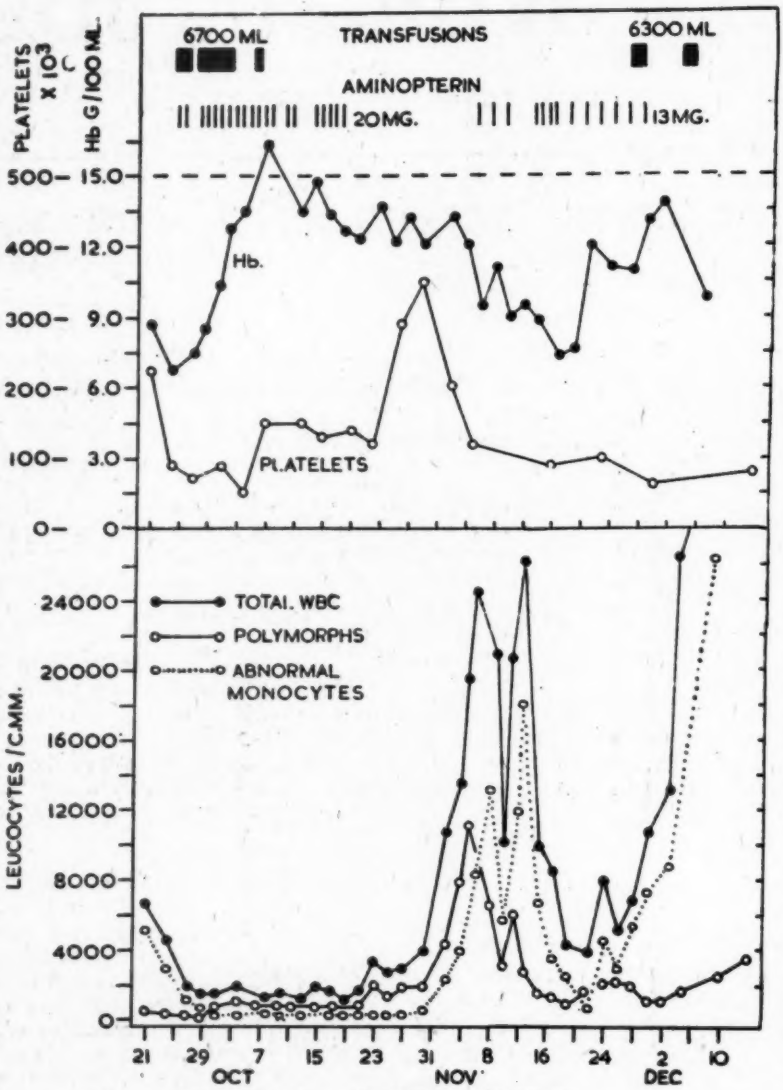

FIG. A.—Case 1. Treatment and progress.

A second course of aminopterin was started on November 5 because of a rising total white cell count with a diminution in the proportion of mature polymorphs and the appearance in the blood of primitive granulocytes. Vertebral puncture then showed that the marrow had become overtly leukaemic again; some 75% of the cells were monocytes of varying degrees of differentiation, with a few developing granulocytes and erythrocyte precursors. By November 27 a further 13 mg. of aminopterin had been given, and two more transfusions. The total white count was then within normal limits, but the proportion of abnormal mononuclears was still high and 5–6% of blast cells and myelocytes were present. The patient's general condition, however, was well enough to allow him to be discharged home on November 28, at which time there was some improvement in the marrow picture.

On December 13 he was readmitted because of haematemesis, generalized purpura, faucial angina, and ulcero-necrotic gingivitis. All superficial lymph nodes, liver, and spleen were greatly enlarged. He died that day from an intracerebral haemorrhage. The white cell count was 320,000 per c.mm., the majority of cells being abnormal monocytes and blast cells.

At necropsy the body was covered with a petechial rash. There was generalized moderate enlargement of lymph nodes and of the lymphoid tissue in the large intestine. The spleen (1,440 g.), liver (5,000 g.), and kidneys were all greatly enlarged, and the appendix was infiltrated with whitish tissue. Histologically, these changes were due to infiltration of the organs with leukaemic cells having the character of monocytes. The bone marrow was generally red and the femur was filled with reddish marrow from end to end. There were a number of thromboses in the vessels of the white matter of the brain and small haemorrhages in both occipital lobes and in the right temporal and frontal lobes. Many small vessels in all the organs were plugged with leukaemic cells, and scattered haemorrhages were fairly numerous. The liver showed extensive leukaemic infiltration of the sinusoids and portal tracts. A similar perivascular infiltration was found in other organs, notably the lungs.

Comment. — The initial response to treatment was a clinical and haematological remission lasting five weeks. During this period a considerable reduction in the proportion of leukaemic cells in the bone marrow was reflected in the peripheral blood, in which abnormal monocytes decreased in number while platelets and mature granulocytes rose to normal levels. When he subsequently relapsed aminopterin proved of no value.

Case 2. Acute Myeloblastic Leukaemia

This patient* was a girl aged 3 years 9 months. Early in September, 1948, her mother observed the gradual onset of swelling and discoloration around both eyes, together with drowsiness, loss of energy, and anorexia. These symptoms became more pronounced and she began to vomit. On September 30 she was admitted to another hospital, where she was found to be febrile and to have generalized enlargement of lymph nodes. During the next three weeks her condition deteriorated, the eyes and face swelling beyond recognition. She was transferred to Hammersmith Hospital on October 20 as a case of acute leukaemia.

*This patient and Case 3 were transferred to our care through the courtesy of Dr. R. E. Bonham-Carter.

J. V. DACIE, E. DRESNER, D. L. MOLLIN, AND J. C. WHITE: AMINOPTERIN IN ACUTE LEUKAEMIA

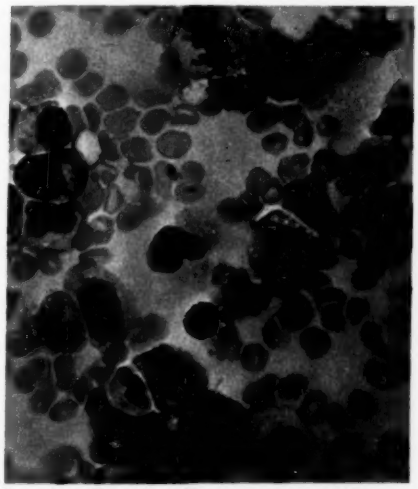

FIG. 1.—Case 1. Bone-marrow smear on admission. (× 400.)

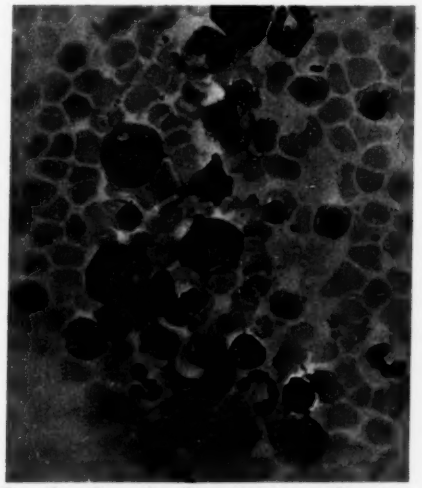

FIG. 2.—Case 1. Bone-marrow after first course of aminopterin. (× 400.)

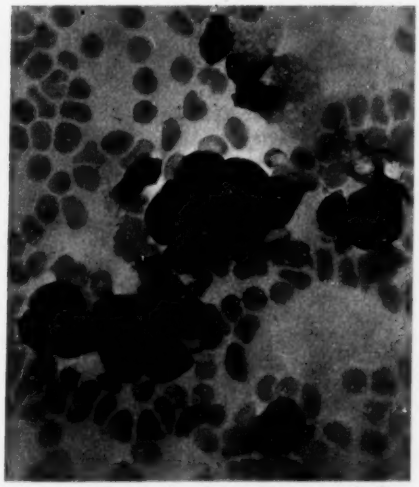

FIG. 3.—Case 4. Bone-marrow before aminopterin treatment. (× 470.)

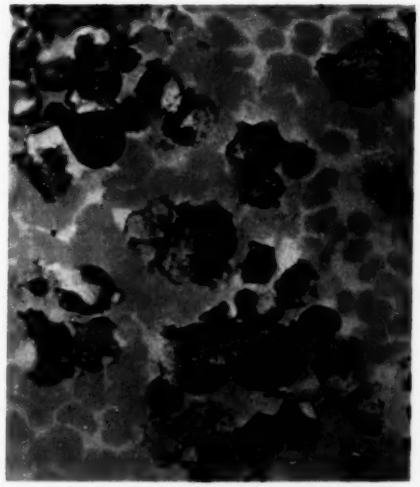

FIG. 4.—Case 4. Bone-marrow after first course of treatment. (× 470.)

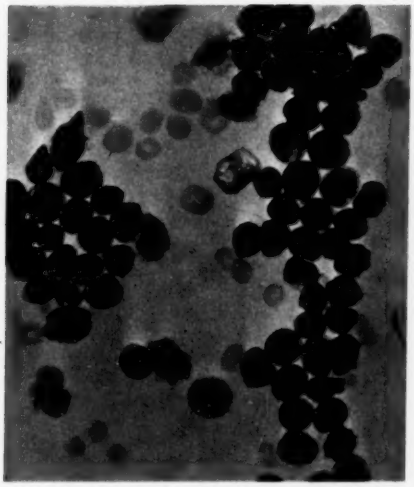

FIG. 5.—Case 5. Bone-marrow before treatment. (× 470.)

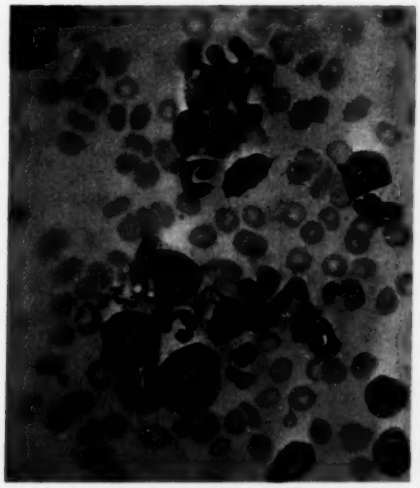

FIG. 6.—Case 5. Bone-marrow after treatment. (× 470.)

PETER STORY: HISTOLOGICAL REACTIONS TO INJECTIONS OF PROCAINE PENICILLIN IN OIL

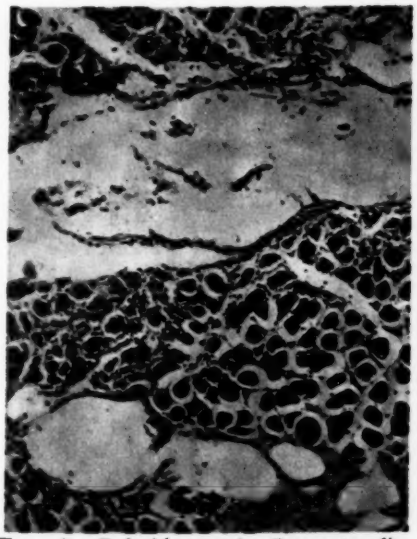

FIG. 1.—Deltoid muscle (haematoxylin-eosin): oil cysts, muscle degeneration, and oedema. (× 65.)

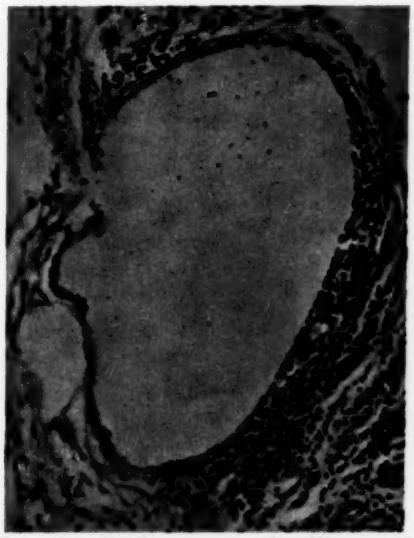

FIG. 2.—Degenerate muscle fibres and cellular reaction round oil droplet in deltoid muscle; H.-E. (× 125.)

FIG. 3.—Oil globule surrounded by foam cells and a multinucleate giant cell; H.-E. (× 300.)

E. WILSON HALL, A. GEOFFREY SHERA, AND E. OWEN FOX: CARCINOMA SIMULATING HERNIA

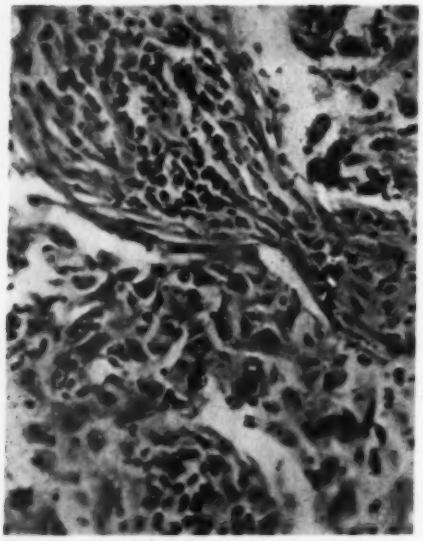

FIG. 1.—Inguinal gland. Mitoses, vesiculation, and inflammatory cells; remnants of lymphoid tissue. (× 220.)

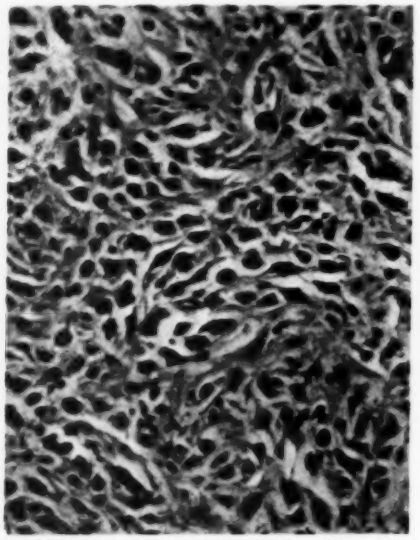

FIG. 2.—Inguinal gland. Oat cells. The hyper-chromatic nuclei are almost universal. (× 290.)

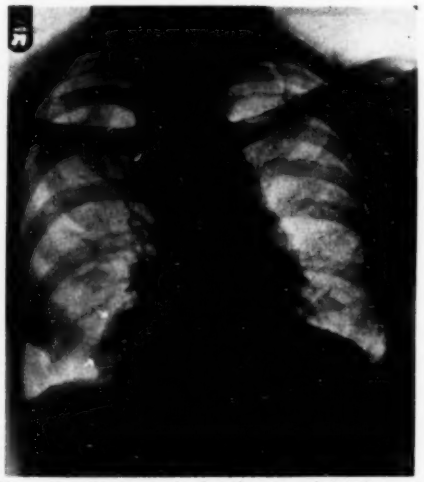

FIG. 3.—Increased density in right lower lobe; probable bronchial carcinoma. Adhesions are present at the left costophrenic angle.

G. SMITH: EFFECT OF DIATHERMY CURRENTS ON METAL IMPLANTS

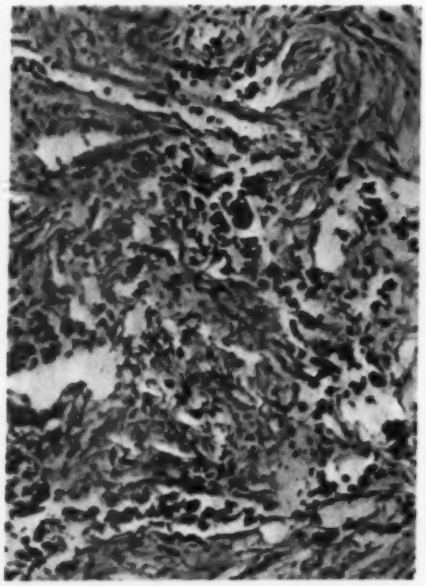

FIG. 4.—Primary growth of right lung (lower lobe). (× 100.)

FIG. 1.—Site of implant (tantalum gauze). (× 30.)

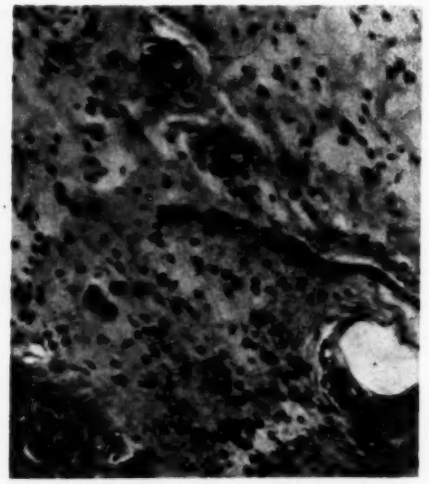

FIG. 2.—Tissue reaction to implant (tantalum gauze). (× 200.)

A. M. BOYD AND R. P. JEPSON: EXTERNAL ILIAC ARTERY THROMBOSIS

FIG. 1.—Case 2. Haematoxylin and eosin. (× 12.)

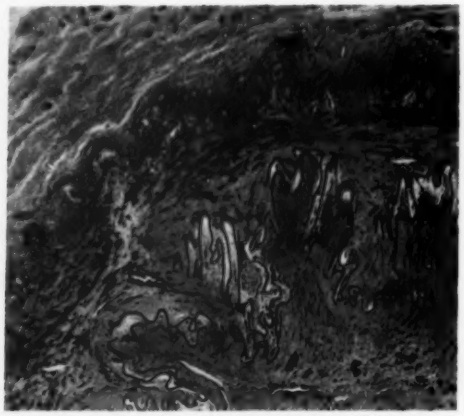

FIG. 2.—Case 2. Haematoxylin and eosin. (× 60.)

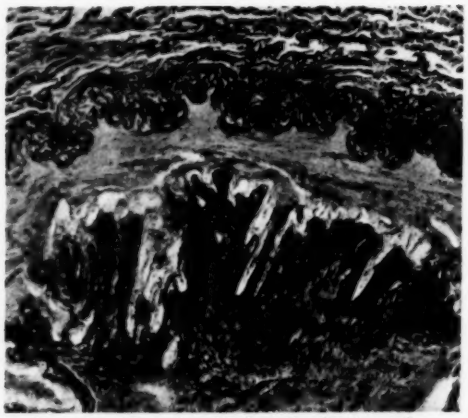

FIG. 3.—Case 2. Weigert's elastic stain. (× 60.)

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On admission the child was pallid, wasted, and febrile. Weight 34 lb. (15.4 kg.). There was marked enlargement of both parotid and submandibular salivary glands, but the most striking features were tense swellings of both upper and lower lids, which were discoloured and purple (Fig. B). The conjunctivae were injected and chemotic, but there was no proptosis and ocular movements were full. The skin, mouth, and throat were healthy. All the superficial lymph nodes were moderately enlarged. The liver and spleen were not palpable. Other systems were normal, as were the urine and radiograph of the chest. A blood count showed: red cells, 2,800,000 per c.mm.; haemoglobin, 8.3 g. per 100 ml.; platelets, 200,000 per c.mm.; white cells, 17,000 per c.mm. (polymorphs 10%, eosinophils 1%, lymphocytes 38%, monocytes 10%, blast cells 8%, neutrophil myelocytes 3%, "smudge" forms 30%).

FIG. B.—Case 2. Periorbital leukaemic infiltrations. Before treatment. October 20, 1948.

Marrow Biopsy.—Marrow was aspirated from the head of the tibia. The majority of the cells were primitive, with deeply basophilic agranular cytoplasm, and were considered to be myeloblasts. There was little, if any, differentiation from normal erythropoiesis or leucopoiesis.

Treatment and Progress

Five intramuscular injections of 1 mg. of aminopterin were given between October 22 and 30, and two blood transfusions, each of 560 ml. Oral penicillin was also given. The result was a rapid fall in the total white cell count to 650 per c.mm. on November 1, and thereafter a steady rise to normal levels. During the leucopenic phase all types of white cells were depressed, but with the rising count mature polymorphs increased to 72% of the total, and immature granulocytes disappeared from the blood.

FIG. C.—Case 2. Resolution of periorbital leukaemic infiltrations following treatment. November 5, 1948.

Marrow biopsy two weeks after discontinuation of aminopterin showed that leucopoiesis and erythropoiesis were taking place normally and that reticulum and stem cells were substantially reduced in the marrow. The haemoglobin rose spontaneously to 15.5 g. by November 22 and platelets rose concurrently to 380,000 per c.mm. There was subjective and objective clinical improvement; the temperature subsided, lymph-node enlargement resolved, and the weight rose, but the most striking improvement was in the condition of the eyes.

By November 5 the periorbital leukaemic infiltration had disappeared and the eyes appeared normal (Fig. C) except for a residual keratitis with an hypopion ulcer on the right side. A further 3 mg. of aminopterin was given during November 25–27 because of a rise in total leucocytes to 23,000 per c.mm. and a slight relapse in the condition of the eyes. After this she improved enough to be discharged on December 6 (Fig. D). The patient was seen again on December 13, when she appeared fairly well; but a week later she died at home suddenly following a convulsion. Death was thought to be due to acute uraemia.

At necropsy (Dr. A. G. Sheara) the significant findings were enlargement of the kidneys (224 g.), which were infiltrated with white nodules, and there were similar infiltrations in the pancreas and gastric mucosa. The liver and spleen were not enlarged and appeared normal to the naked eye, and there was moderate enlargement of the mesenteric glands.

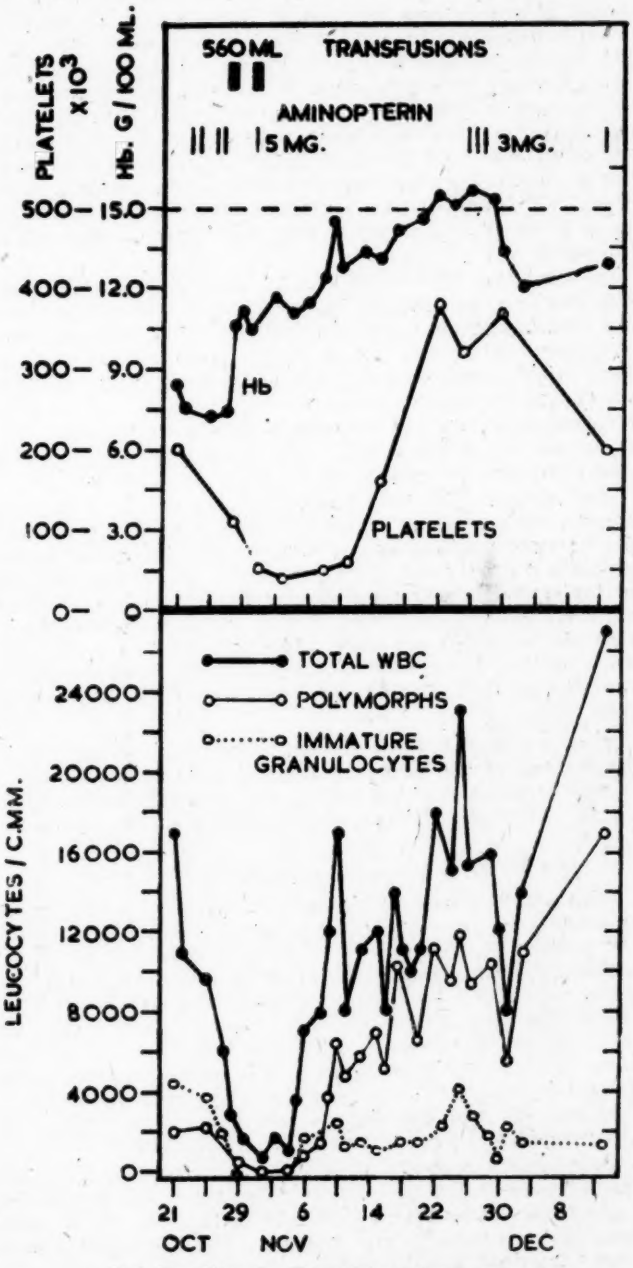

FIG. D.—Case 2. Treatment and progress.

Histologically, the kidneys, stomach, pancreas, and mesenteric nodes were infiltrated with large round mononuclear cells, showing numerous mitoses. Surprisingly, sections of the vertebral marrow showed well-differentiated actively erythropoietic and leucopoietic tissue, with only a slight excess of primitive cells, in marked contrast to the visceral lesions and to the pre-treatment aspiration biopsy.

Comment.—The remission induced in this case was dramatic, though short-lived, and necropsy revealed that, though the leukaemic process seemed to have been largely eradicated from the bone marrow, visceral infiltration was nevertheless pronounced.

Case 3. Subacute Lymphoblastic Leukaemia

A boy aged 3 years first complained of stiffness of the back on November 23, 1948. A week later he also complained of pain in both legs, and by December 20 was unable to walk owing to pain and stiffness of the spine and legs and was anorexic and very pale. He was admitted to another hospital, where he was found to be anaemic, with generalized enlargement of lymph nodes; and radiological bone changes were found in the lumbar spine and right femur. The white cell count was 3,000 per c.mm., with 86% lymphocytes, and sternal puncture showed that the cells in the marrow were almost all lymphoblasts. He was transferred to Hammersmith Hospital on January 1, 1949, as a case of aleukaemic leukaemia.

On admission he was seen to be an intelligent child, but pale and anorexic. Weight 29 lb. (13.2 g.). The skin, throat, and mouth were clear, and the liver and spleen were not felt. No abnormalities were found in the other systems. Some small lymph nodes were palpable in the neck, but none elsewhere, and the salivary glands were not enlarged. There was no bone tenderness, but the dorsolumbar spine was rigid and movement was resisted. He could stand only with support. The urine and radiographs of the chest were normal.

Radiographs of the long bones and spine revealed a pseudofracture with adjacent periosteal elevation at the upper end of the right humerus and a similar condition in the metaphysis at the lower end of the right femur. There was collapse of the second lumbar vertebra with anterior wedging. Other vertebrae and long bones were normal. A blood count showed: red cells, 4,600,000 per c.mm.; haemoglobin, 11.1 g. per 100 ml.; platelets, 340,000 per cmm.; white cells, 5,800 per c.mm. (polymorphs 32%, lymphocytes 63%, monocytes 2%, plasma cells 3%).

Marrow Biopsy.—The upper end of the tibia was punctured. About 90% of the total cells were of the lymphocyte series, mostly lymphoblasts, but with some differentiation to adult forms. The picture was that of lymphoblastic leukaemia.

Progress and Treatment

Two short courses of aminopterin, each of 1 mg. intramuscularly for four days, were given between January 10 and 21. This was followed by a moderately severe ulcerative stomatitis which lasted eight days. He then developed a respiratory infection and consolidation of the left lower lobe, which was treated with sulphadimidine. By the middle of February his chest was clear, he was afebrile, and there was great symptomatic improvement. His appetite returned and he gained weight. The glandular enlargement in the neck had resolved and the stiffness and pain in the spine had disappeared and he was able to walk unaided.

Radiographs showed healing of the fracture of the right humerus, resolution of the osteitis at the lower end of the right femur, and a return to normal architecture in the structure of the second lumbar vertebra. The haemoglobin level was maintained, and the white count was 7,000 per c.mm. with 50% polymorphs, and no immature cells were present. The platelet count rose to 400,000 per c.mm. Tibial puncture on March 2 showed active leucopoiesis, but without evidence of leukaemia, blast cells forming less than 1% of the total, and erythroblasts, granulocyte-precursors, and megakaryocytes were present in normal numbers. He was discharged home active, and with no abnormal signs, on February 23.

He was seen again on April 14, when he appeared clinically well, with a haemoglobin of 15.5 g. per 100 ml. and a normal blood count, but sternal puncture revealed a resurgence of the leukaemic process in the marrow, some 35% of the cells being lymphocytes of varying maturity, of which half were nucleolated blast cells. He was readmitted, and 9 mg. of aminopterin was given orally from May 7 to 16. His general condition remained good during treatment. The white cell count, 13,000 per c.mm. on admission, fell to 3,000 per c.mm., with 30–40% polymorphs and 50–60% lymphocytes. He was discharged on May 30, clinically well, weighing 33 lb. (15 kg.). The bone pattern was still radiologically normal at all the sites of previous infiltration. He remained well throughout the summer, but his condition began to deteriorate towards the end of August.

When admitted for the third time on August 29 he was found to have lost weight, and his liver, spleen, and lymph nodes were found to be enlarged. Anaemia, thrombocytopenia, and granulocytopenia were present; of 5,000 white cells per c.mm., only 3–4% were polymorphs. Moderate numbers of lymphoblasts were present. The bone marrow was leukaemic. A third course of aminopterin totalling 12 mg. was given, during which time his condition continued to deteriorate. He died on September 19, three days after treatment was discontinued, following a short bout of diarrhoea and vomiting.

At necropsy there was generalized lymph-node enlargement, histologically marked by sheet-like growth of leukaemic lymphocytes in the medullary stroma, congestion of capillaries, and some areas of cellular degeneration and depletion; the reticulum cells of the follicles were hyperplastic and degenerate, the splenic Malpighian bodies being affected similarly. The bone marrow was red and gelatinous, crowded with leukaemic cells and primitive stem cells, and showed areas of haemorrhage, cellular degeneration and depletion, and oedema of sinusoids. A 20-cm. segment of the jejunum was the site of haemorrhagic necrosis, with adjacent oedema and prominence of lymphoid tissue.

Comment.—The initial response to aminopterin was most satisfactory from both clinical and haematological aspects. Primitive stem cells were reduced from about 90% to less than 1% in the marrow, radiological changes in the spine and long bones disappeared, and clinically he became indistinguishable from normal. On the second occasion the response to aminopterin was less satisfactory from the haematological point of view, but he remained well until his final relapse some nine months from the onset of symptoms.

Case 4. Myeloblastic Leukaemia

A boy aged 2 years began to lose weight and appetite in October, 1948, and became unsteady on his legs and increasingly pale. On November 4 he was admitted to another hospital for investigation of anaemia and was transfused, but was discharged on November 25 because he developed mumps. On December 28 he was admitted to a second hospital with general weakness, inability to walk, and marked pallor. He was there found to be febrile and anaemic, with generalized enlargement of the lymph nodes. On the evidence of blood examination and marrow biopsy a diagnosis of aleukaemic leukaemia was made and he was transferred for treatment on January 1, 1949.

On admission he was found to be febrile and pale, with no purpura or icterus. Weight 25½ lb. (11.5 kg.). No abnormality was found in the throat or in the respiratory, cardiovascular, and central nervous systems. Firm enlarged glands were felt in the neck, but none elsewhere. The edge of the liver was just palpable, but the spleen could not be felt. A radiograph of the chest was normal and there was no abnormality in the urine. A blood count showed: red cells, 1,900,000 per c.mm.; haemoglobin, 3.7 g. per 100 ml.; platelets, 131,000 per c.mm.; white cells, 4,600 per c.mm. (polymorphs 9%, lymphocytes 91%).

Marrow Biopsy.—The head of the tibia was punctured; 90% of the cells were blast cells with scanty basophilic cytoplasm, stippled nuclear chromatin, and one or more nucleoli. Only a few lymphocytes and erythroblasts were seen. The appearance was that of myeloblastic leukaemia (Plate, Fig. 3).

First Admission

A transfusion was given on January 2. The haemoglobin rose to 11.5 g., and thereafter this level was maintained. During the first two weeks seven 1-mg. injections of aminopterin were given. Throughout January his condition was poor; he vomited persistently, became very dehydrated, and developed a left basal pneumonia. However, by February 1 he was much improved; his chest was normal and pyrexia had subsided. His appetite increased, his weight rose, and he was allowed up. The cervical glands and spleen were no longer palpable. The white cell count at this time was

Second Admission

The patient remained well until readmitted on April 24 with a four-days history of anorexia, vomiting, and the passage of blood in the stools. He appeared well nourished and was not anaemic, but small glands were felt in the neck, axillae, and groins, and the liver and spleen were palpable 1 in. (2.5 cm.) below the rib margins. The white cell count was 28,000 per c.mm., with 72% myeloblasts and only 3% mature granulocytes, and the platelets had fallen to 21,000 per c.mm. Aspiration of the marrow showed once more an almost complete replacement by myeloblasts and micromyeloblasts.

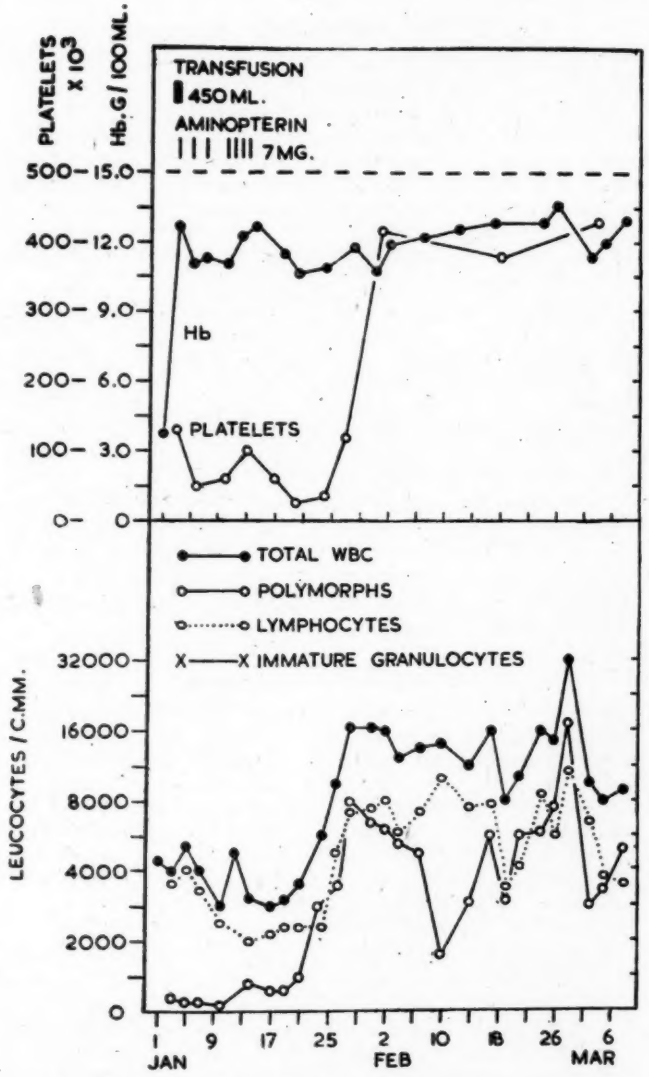

FIG. E.—Case 4. First admission. Treatment and progress.

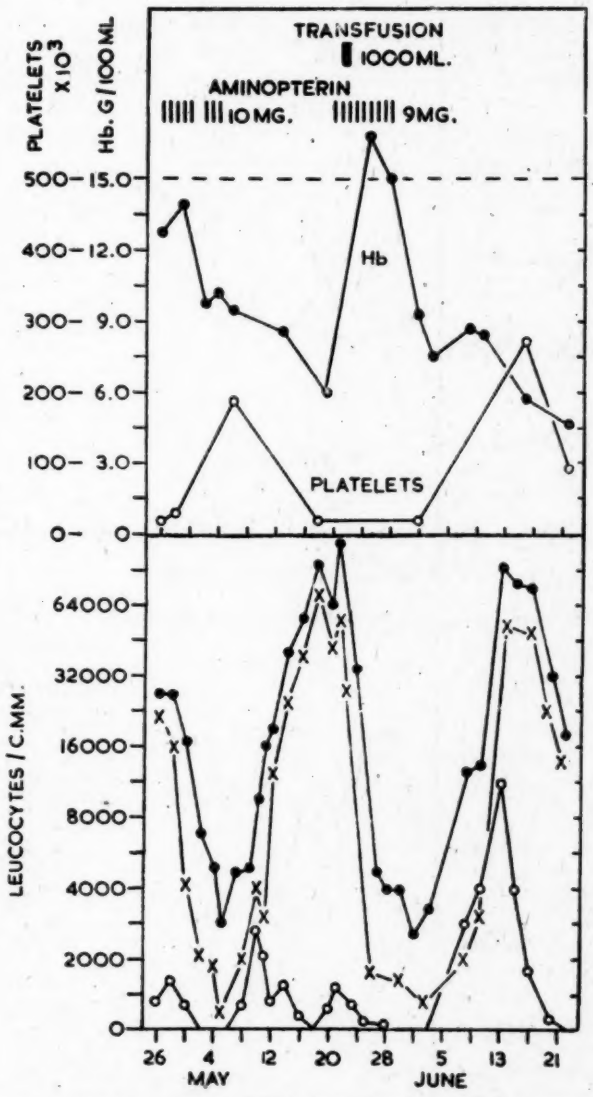

FIG. F.—Case 4. Second admission. Treatment and progress.

10,000 per c.mm., of which 42% were mature polymorphs, and no abnormal cells were present. The platelets had risen to 417,000 per c.mm. Tibial puncture at the end of January revealed a marrow that was almost indistinguishable from normal. There was active leucopoiesis and erythropoiesis, with blast cells forming only 3% of the total and a normal proportion of segmented neutrophils and normoblasts (Plate, Fig. 4, and see Fig. E, above).

During March he remained well in spite of an upper respiratory infection and parotitis, and when discharged on March 9 he was active, had no abnormal signs, and weighed 27 lb. (12.2 kg.). The white cell and platelet counts were normal, and aspiration of the marrow revealed no positive evidence of leukaemia.

Aminopterin, 10 mg., was given by mouth in the course of ten days and at the end he was miserable, slightly febrile, and completely anorexic. The liver, however, was no longer palpable and only the tip of the spleen could be felt. Enlargement of lymph nodes had diminished. The white cell count fell to 3,000 per c.mm. on May 5; only 2% of the cells were blasts, but no polymorphs could be found and the platelets remained very low. His general condition improved, but by May 20 the white cell count had risen to 122,000 per c.mm. and the liver and spleen were re-enlarging rapidly (Fig. F, above).

A third course of oral aminopterin and a small transfusion were given, with the result that the white cell count was again markedly depressed, but blast cells persisted in the blood and

polymorphs remained absent. As before, there was a temporary diminution in the size of the liver and spleen, but two weeks later a complete relapse occurred and he died on June 24. Both courses of treatment during this admission were complicated by buccal stomatitis.

At necropsy the hyperplastic bone marrow was red in colour and crowded with small primitive cells and cells evidently

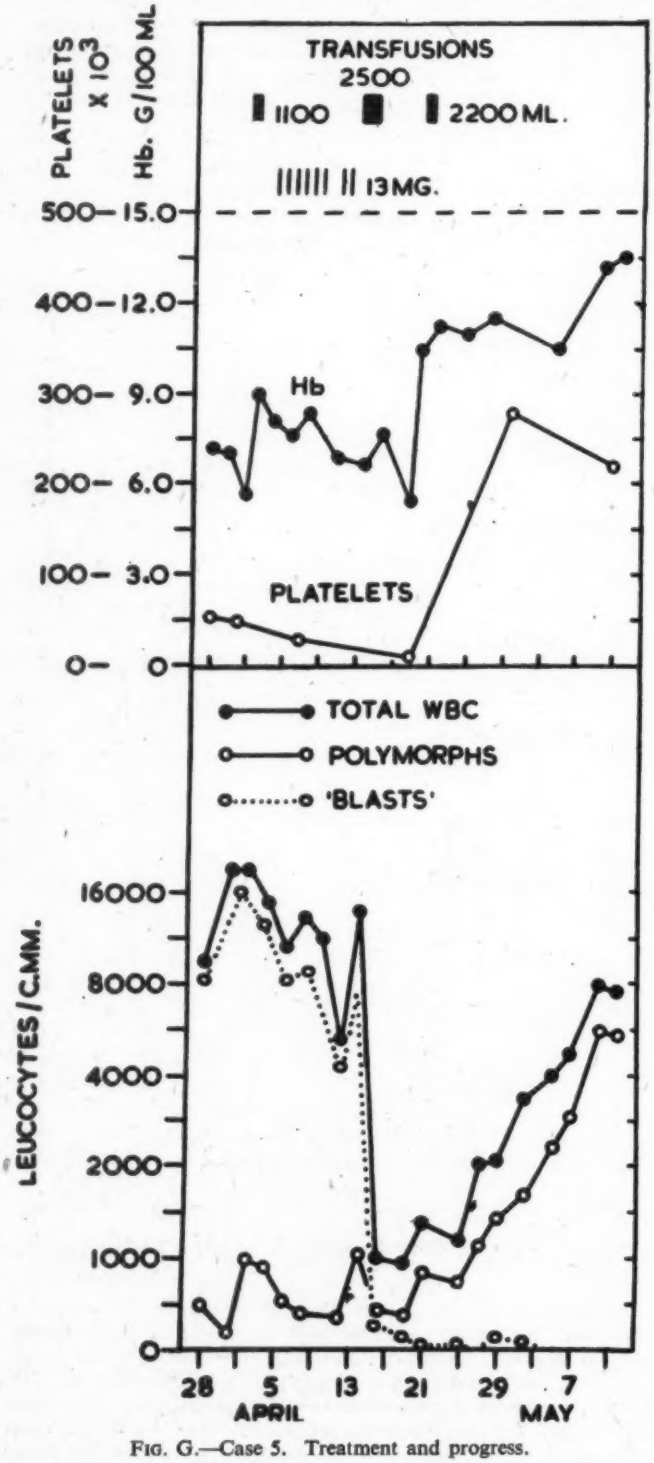

FIG. G.—Case 5. Treatment and progress.

belonging to the granulocyte series. Several groups of lymph nodes were enlarged, their medullary stroma having a cellular composition similar to that of the bone marrow and spleen. The liver showed periportal, and the kidneys perivascular, leukaemic infiltration. The pharynx was affected by acute necrotizing inflammation. A 17-cm. length of terminal ileum was the site of mucosal necrosis and oedema without significant leukaemic infiltration; neighbouring Peyer's patches were ulcerated, and were infiltrated by leukaemic cells.

Comment.—When first admitted, a relatively small amount of aminopterin caused a reversion almost to normal in the state of the bone marrow and peripheral blood and a clinical remission of about three months. When he relapsed two larger courses of the drug each induced a pronounced though transient depression of the leucocyte count with some diminution in the size of the spleen, but without a corresponding improvement in the marrow and without any sustained clinical benefit.

Case 5. Acute Myeloblastic Leukaemia

A schoolboy aged 13 was referred to his doctor early in March, 1949, because of increasing pallor. There was no bleeding or bruising, and he was attending school. He was admitted to a hospital for investigation and was found to be severely anaemic, with an enlarged spleen and liver. The leucocyte count varied from 10,000 to 18,000 per c.mm., most of the cells being immature, and a diagnosis of acute leukaemia was confirmed by marrow biopsy. He was transfused, and on March 25 was transferred to Hammersmith Hospital for further treatment.

On admission he was found to be an intelligent active boy, but very anaemic. There was no purpura and the mouth and throat were normal. The tonsillar glands were palpable, but no other glands were felt. The liver and spleen were palpable 1 in. (2.5 cm.) below the costal margins. Other systems were normal. Weight 88 lb. (39.9 kg.). Temperature 99.6° F. (37.55° C.). A radiograph of the chest was negative. A blood count showed: red cells, 2,000,000 per c.mm.; haemoglobin, 6.1 g. per 100 ml.; platelets, 55,000 per c.mm.; white cells, 10,000 per c.mm. (blast cells 79%, polymorphs 5%, lymphocytes 15%, monocytes 1%) (see Fig. G).

Marrow Biopsy.—Sternal puncture showed the marrow to be replaced by primitive cells having the characteristics of micromyeloblasts (Plate, Fig. 5).

Progress and Treatment

During the first week after admission he had frequent small epistaxes, and was given a blood transfusion on April 1, which raised his haemoglobin to 8.9 g. A total of 13 mg. of aminopterin was given by mouth from April 4 to 12. Towards the end of treatment he had severe and repeated epistaxes, and was transfused three times; the total volume of blood given was 4.7 litres. He also developed a moderately severe vesicular stomatitis lasting one week, for which he was given parenteral penicillin. By April 23 epistaxes had ceased and, his condition being much improved, he was allowed up.

He was discharged home on May 10, free of symptoms. The liver and spleen were no longer palpable, and no glands could be felt. He was normally active and had gained 5 lb. (2.3 kg.) in weight since admission. Aminopterin had caused a fall in the total white cell count to 930 per c.mm. on April 22. The leucopenic phase lasted about one week, and then the white cell count rose to normal levels. Blast cells and immature granulocytes disappeared from the blood, and at the time of discharge he had 8,000 leucocytes per c.mm., of which 67% were polymorphs, and his platelets were 200,000 per c.mm. The bone marrow had been transformed. On April 23 there were few recognizable blast cells present, and granulopoiesis and erythropoiesis were active. On May 6, although a few myeloblasts were present, developing granulocytes and erythroblasts were well represented, and megakaryocytes were abundant (Plate, Fig. 6).

The patient was readmitted on May 31 because marrow biopsy showed an increased proportion of primitive cells and about 20% of the leucocytes in the peripheral blood were blast cells. Between June 1 and 16, 17 mg. of aminopterin was given by mouth. The drug was then discontinued because of severe and intractable epistaxis. His haemoglobin fell to

6.1 g. and another transfusion was required. The changes in the blood and bone marrow were not so dramatic as on the first occasion. The total white cells fell to 3,700 per c.mm. on June 22, and thereafter remained steady at about 8,000 per c.mm. There was some reduction in the number of circulating primitive cells and a rise in the proportion of polymorphs, but blast cells were not entirely removed, either from the blood or from the bone marrow. In view of the severe bleeding, further treatment at that time was considered inadvisable, and he was discharged home on July 2, free of symptoms and with no glandular or splenic enlargement but with a slight fall in weight. A month later he was readmitted, severely anaemic and with a very large spleen. Again treatment with aminopterin had to be abandoned owing to almost continuous epistaxis after only 6 mg. had been given. He died on August 11. Necropsy was not performed.

Comment.—Aminopterin in this case produced a marked remission on the first occasion it was used, but when the patient relapsed a few weeks later treatment had to be abandoned because of severe epistaxis, and the improvement in the blood and bone marrow was much less striking. On the third occasion continuous epistaxis virtually precluded further attempts at treatment.

Case 6. Subacute Myeloblastic Leukaemia

A 47-year-old housewife first consulted her doctor in August, 1948, because of pallor, dyspnoea on exertion, and weakness, symptoms which became progressively more severe during the next five months, and to which were later added palpitations, swelling of the ankles, and loss of weight. There was no external bleeding and the menses were regular. On February 3, 1949, she was admitted to another hospital, where she was found to be very anaemic and to have a white cell count of 39,000 per c.mm., of which the majority were immature granulocytes. She was transfused, and on February 7 was transferred to Hammersmith Hospital as a case of myeloblastic leukaemia.

On admission she was febrile and very pale, but apart from a recent haemorrhage in the left fundus there were no external signs of bleeding and no icterus. The throat, mouth, and gums appeared normal and there were no palpable glands. The tip of the spleen was just palpable; the liver was not felt. No abnormalities were apparent in the lungs or in the cardiovascular and central nervous systems. The urine and radiographs of the chest were normal. A blood count showed: red cells, 1,600,000 per c.mm.; haemoglobin, 5.3 g. per 100 ml.; packed cell volume, 16%; platelets, 100,000 per c.mm.; white cells, 40,000 per c.mm. (blast cells 28%, promyelocytes 2%, neutrophil myelocytes 4%, metamyelocytes 8%, polymorphs 35%, lymphocytes 16%, monocytes 1%, "smudge" forms 6%).

Marrow Biopsy.—Marrow was aspirated from the spinous process of a lumbar vertebra. The picture was of subacute myeloid leukaemia; 25% of the cells were myeloblasts and most of the remainder developing granulocytes. A few lymphocytes were present, but erythroblasts were very scanty and no megakaryocytes were seen.

Treatment and Progress

Soon after admission penicillin therapy was started, and she was transfused on February 21 and 28, with the result that the haemoglobin was raised to 14.7 g. During her first ten days under observation she developed a further haemorrhage into the left fundus, septic lesions at the transfusion sites on the left arm and ankle, and ulcerative lesions of the lips with a marked tendency to bleed.

Aminopterin, 34 mg., was given intramuscularly in 2-mg. daily doses between March 1 and 9. A generalized purpuric rash developed and she bled from ulcers on the lips, nose, transfusion sites and vertebral puncture site, and haematomata formed at the sites of penicillin injections. Spreading superficial ulceration developed on both forearms and legs and over the sternum. The throat, tonsils, and tongue became ulcerated and there was severe menorrhagia, which was partially controlled by large doses of stilboestrol. The spleen enlarged and the liver became palpable. She continued febrile and anorexic and her weight fell. A third transfusion was given on March 16 as the haemoglobin had fallen to 4.6 g.

The effect of aminopterin on the peripheral blood was a steady fall in the white cell count to 3,800 per c.mm. on March 21 and thereafter a rise to 17,000 per c.mm. a week later, following which the total white count remained at normal levels till death. There was at first no change in the differential count, but about April 1 the proportions of blast cells and immature granulocytes fell, and that of the polymorphs rose. On April 16, a week before death, 54% of 5,000 total white cells were polymorphs and only

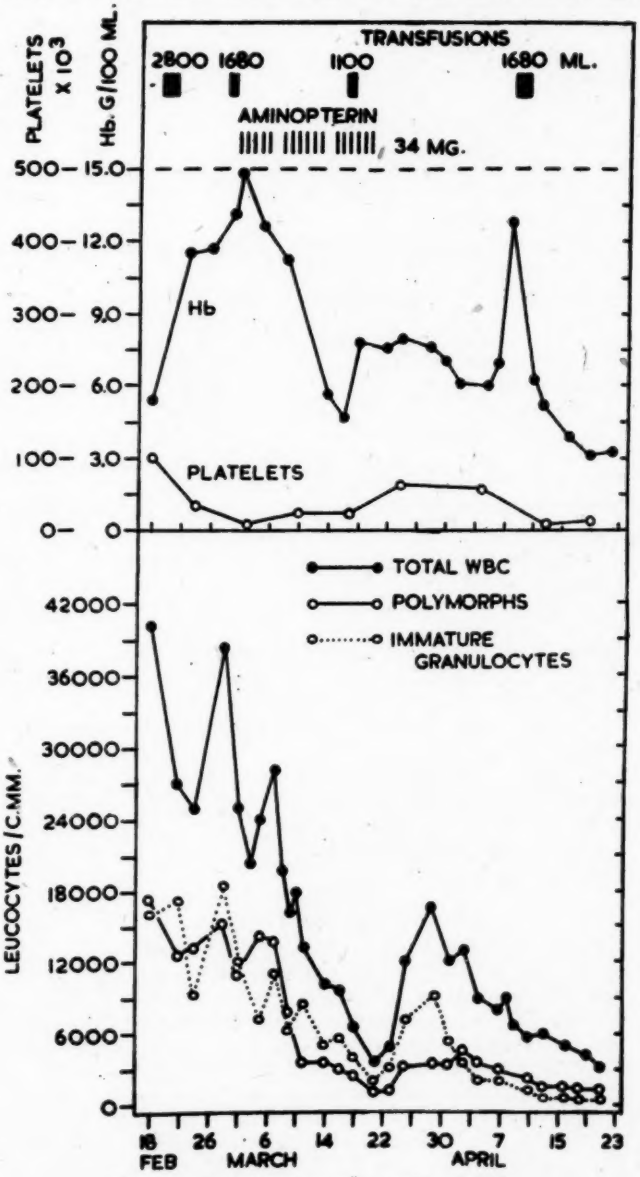

FIG. H.—Case 6. Treatment and progress.

11% were immature cells. As will be seen (Fig. H), platelets remained very low or absent during the whole illness.

After discontinuation of aminopterin, cutaneous ulceration healed, sloughs in the mouth separated, and the fundal haemorrhages were absorbed, but the patient remained anorexic and became increasingly cachectic. She was transfused again on April 7, but on April 10 there was a severe rectal haemorrhage lasting several days which almost exsanguinated her. Further transfusions were refused. The haemoglobin fell to 3 g. and she died on April 22. Necropsy was not performed.

Comment.—The history in this case was fairly long-standing and the course was downhill from the start of

treatment. The effect of aminopterin on the blood was to reduce the total white cell count to normal levels with an increase in the maturity of the granulocytes, but the thrombocytopenia was uninfluenced, and the haemorrhagic manifestations ultimately proved fatal.

Case 7. Subacute Lymphoblastic Leukaemia

A schoolboy aged 7 developed painful red swellings of both elbows, with malaise and low fever, early in November, 1948, and during the next four weeks had migratory painful swellings of the elbows, wrists, knees, and ankles, and occasionally of the face, and was pale and sweating. A diagnosis of acute rheumatism was made. On March 11, 1949, he was admitted to a hospital for incision of an abscess of the buttock, but fever persisted and he complained of pain in the limbs, although there were no further joint swellings. He was anorexic and pallor increased. Investigation of the blood and bone marrow led to the diagnosis of an acute stem-cell leukaemia, and radiographs showed bone changes in the left humerus. He was transfused and transferred for treatment on April 14, 1949.

On admission he was thin, with a good colour but in obvious pain. Temperature 99.4° F. (37.4° C.). Weight 42 lb. (19 kg.). There was no purpura or bleeding, and his mouth and throat were healthy. Small mobile lymph nodes were palpable in the neck, axillae, groins, and epitrochlear regions. Salivary glands were not enlarged, and the liver and spleen were not palpable. The heart and lungs were normal. The upper third of the shaft of the left humerus was tender and movements of the left shoulder and elbow were restricted. The left knee was held semiflexed and all movements were extremely painful. There was marked tenderness over the lower end of the femur and gross wasting of the quadriceps, but no effusion into the joint.

X-ray Examination.—Radiologically the chest was normal. There was periostitis throughout the length of the left humerus and considerable cortical destruction of the upper third resulting in a pathological fracture. The femora and left knee showed no change, but there was a wedge deformity of the ninth dorsal vertebral body. The *x*-ray appearances were consistent with leukaemic infiltration of bone.

A blood count showed: red cells, 4,200,000 per c.mm.; haemoglobin, 13.5 g. per 100 ml.; platelets, 70,000 per c.mm.; white cells, 2,500 per c.mm. (polymorphs 5%, lymphocytes 86%, blast forms 8%, monocytes 1%).

Marrow Biopsy.—On sternal puncture the marrow was very cellular. The great majority of the cells were blast forms, considered to be lymphoblasts.

Progress and Treatment

During the first week he was febrile and ill, with constant severe pain in the left knee and arm. Aminopterin, 13 mg. in daily doses of 1 mg. by mouth, was given from April 22 to May 5. The bone pains ceased after five doses of aminopterin, but treatment was complicated by a haemorrhagic stomatitis, and a fall in haemoglobin to 4.5 g. necessitated a transfusion. After this episode he became afebrile, and a general improvement began which was maintained until his discharge. Tenderness of the left knee and arm disappeared within three weeks and he was able to move his shoulders, elbows, and knees freely, and he began to walk. His appetite returned and his weight increased. The immediate effect of treatment on the blood was a reduction in the total leucocyte count to 800 per c.mm. on May 12 and thereafter a rise to normal levels. Sternal puncture on June 9 showed that while 60% of the cells were lymphocytes, most were mature, and only 6% were blast cells. Developing granulocytes and erythroblasts were well represented.

A second course of aminopterin totalling 8 mg. was given from June 14 to 21 without untoward effect, and when he was discharged home on June 28 he was walking fairly well, had no palpable glandular or splenic enlargement, and was apparently normal. Radiographs of the left humerus on May 26 showed consolidation of the periosteal new bone with sclerosis of the cortex and union of the fracture previously demonstrated.

On August 9 he was readmitted because of pain in the back. This was found to be due to collapse of most of the dorsal and the second to fifth lumbar vertebral bodies. The bone marrow was again leukaemic. The white blood cell count was 5,000 per c.mm. with only 13% of polymorphs. A third course of aminopterin, totalling 13 mg., produced no improvement in the peripheral blood or in the appearance of the bone marrow, but the bone pain was relieved. After a transfusion of 1,100 ml. of blood a fourth course of 8 mg. of aminopterin by mouth was given. His condition rapidly deteriorated and the total leucocyte count rose to 63,000 per c.mm., of which 80% were lymphoblasts. He died on November 10, with generalized purpura and bleeding from the stomach and rectum.

At necropsy there was generalized enlargement of lymphoid tissue and leukaemic infiltration of the heart, pericardium, pleurae, lungs, spleen, liver, and kidneys. The marrow of the long bones was red and gelatinous. The vertebrae were collapsed and filled with greyish-red marrow and the periosteum over the upper end of the left humerus was greatly thickened by leukaemic infiltration. Microscopically, the bone marrow was found to be very cellular, the normal tissue being replaced by primitive leukaemic cells.

Comment.—Leukaemic bone infiltration was a striking feature in this case. The initial response to treatment was symptomatically and haematologically satisfactory, but increased amounts of aminopterin were without effect when given for his subsequent relapse. At necropsy there were no changes which could be attributed to the treatment.

Case 8. Subacute Lymphoblastic Leukaemia

A girl aged 5½ years first had slight pallor in December, 1948, but it did not become pronounced until after an attack of bronchitis early in January, 1949, when she complained of increasing tiredness, loss of weight, and night sweats. She was admitted to another hospital on February 1 and was found to be severely anaemic with splenomegaly and generalized enlargement of the lymph nodes. The white cell count was 4,200 per c.mm., with a preponderance of lymphocytes; marrow biopsy confirmed the diagnosis of lymphatic leukaemia. During April her condition deteriorated; anaemia and lymph-node enlargement increased and the parotids became swollen. She was transferred on April 29 with the diagnosis of aleukaemic leukaemia.

On admission she was thin and pale, with petechial haemorrhages in the buccal mucosa and ecchymoses of both arms. Temperature 102° F. (38.9° C.). Weight 41 lb. (18.6 kg.). Small hard glands were felt in the neck, axillae, and groins. The parotids and the left submandibular salivary gland were swollen and tender. The spleen was palpable one fingerbreadth and the liver three fingerbreadths below the costal margins. The throat and gums were healthy and no abnormalities were detected in the lungs, heart, or central nervous system.

Radiographs revealed an area of cortical bone destruction, with periosteal elevation at the distal end of the left tibia, and periostitis of the shaft of the first left metatarsal—changes compatible with leukaemic infiltration. A blood count showed: red cells, 2,000,000 per c.mm.; haemoglobin, 7.4 g. per 100 ml.; platelets, 46,000; white cells, 2,700 per c.mm. (polymorphs 32%, lymphocytes 58%, monocytes 4%, plasma cells 6%).

Marrow Biopsy.—The iliac crest was punctured. About 75% of the cells were of the lymphocyte series, the majority being blast cells with one or two nucleoli and uniform cytoplasmic basophilia; a few were mature lymphocytes. The appearance was that of lymphoblastic leukaemia.

Progress and Treatment

A transfusion of 570 ml. of blood on May 5 raised the haemoglobin to 9.7 g. A total of 15 mg. of aminopterin in 1-mg. oral doses was given from May 10 to June 1. Clinical

improvement was noticed after 6 mg. had been taken. She became afebrile, her appetite improved, and she began to walk, but limped slightly on the left foot. At the end of treatment a few small glands were felt in the neck only, and the salivary glands, liver, and spleen were no longer palpable. Her weight had increased and her colour had improved. Radiographs showed no further progress in the bone lesions. The aminopterin had no apparent effect on the peripheral blood; the white cell count remained at 4,000–8,000 per c.mm., with 20–30% polymorphs and 50–60% of mature lymphocytes. Iliac-crest puncture on June 9, however, showed a great reduction in the leukaemic process in the marrow. About half the cells were lymphocytes, but only 1% were as primitive as before treatment, and normally developing granulocytes and erythroblasts were numerous. The patient was discharged home on June 16, and when seen again two months later she weighed 48 lb., was clinically normal in every way, and there were no abnormal cells in the peripheral blood.

However, by the beginning of September there were clinical and haematological signs of relapse. She was admitted and given 7 mg. of aminopterin from September 12 to 18. At the end of treatment there was great improvement, both in her clinical well-being and in the appearance of the bone marrow. She was discharged on September 27 to continue aminopterin as an out-patient, in a dosage of 0.25 mg. by mouth on alternate days.

A month later her haemoglobin had risen spontaneously to 17.2 g. and the platelets to 400,000 per c.mm. There were 15,000 white cells per c.mm., the differential count being normal. She was clinically well and had gained 4½ lb. (2 kg.) in weight. However, at the beginning of December her haemoglobin started to fall, she became anorexic and listless, and a marrow biopsy confirmed that she had relapsed. The dose of aminopterin was increased to 0.25 mg. daily, but without avail. Her peripheral blood became flooded with lymphoblasts, and she died on December 26.

Necropsy revealed a moderate generalized lymph-node enlargement as well as infiltration of the solid viscera with leukaemic cells.

Comment.—This case was aleukaemic from the outset, and aminopterin had little apparent effect on the peripheral blood. Nevertheless, the bone marrow showed a very satisfactory improvement and the clinical effect was good. In its subacute course, clinical picture, with bone involvement, and in its marrow cytology the disease in this child closely resembles that of Case 5, and the initial response to treatment was similar in both cases.

Other Cases

Details of the following patients are presented in summary form through lack of space.

Case 9 was an adult suffering from an advanced stage of acute myeloblastic leukaemia, severely anaemic, and with widespread purpura. His total white cell count fell precipitously after three doses of 3 mg. of aminopterin. He died four days after admission. At necropsy relative hypoplasia of the bone marrow suggested that widespread destruction of marrow tissue had taken place.

Cases 10–12 were adults suffering from subacute paramyeloblastic leukaemia. In one case there was an appreciable improvement lasting approximately four weeks after the first course of therapy; the other two cases failed to respond.

Case 13 was a boy aged 4½ years suffering from lymphoblastic leukaemia. A dramatic remission was observed and he remained well for eight weeks. Subsequent attempts at therapy were, however, of no benefit.

Results

The results of treatment in the 13 cases, tabulated according to age and type of leukaemia, are as follows:

Adults:		
Myeloblastic and paramyeloblastic	5 cases	No improvement in 4; temporary remission in 1
Monocytic	1 case	Temporary remission
Children:		
Myeloblastic ..	3 cases	Temporary remissions in all
Lymphoblastic ..	4 cases	

Remissions have been observed following treatment in each of the seven children, but in only two of the six adults. In the children the remissions have taken the form of an almost complete clinical restoration to normality and in most the peripheral blood has also become normal, or almost so, for a time. Changes in the bone marrow have been striking, but in no case has there been a complete disappearance of the primitive leukaemic cells, and this has no doubt meant that relapse has been inevitable. When relapse has occurred the evidence of this in the blood, and more particularly in the bone marrow, has antedated the clinical symptoms.

The duration of the remissions has varied from a few weeks to several months. The remissions in the two adult cases were partial and very short-lived. In the adults who failed to respond the effect of aminopterin may have been actually harmful, causing an increased tendency to bleed and perhaps increasing the incidence of septic complications.

Dosage and Toxicity

The dosage of aminopterin was largely empirical, but, in general, children were given 1 mg. daily and adults 1–3 mg. daily until there was a pronounced haematological effect or toxic symptoms compelled its withdrawal. The drug was at first given by intramuscular injection, but later it became evident that the therapeutic and/or toxic effects were the same, dose for dose, when given by mouth, and the drug has since been given only by this route. It is readily soluble in water and is almost tasteless.

In the treatment of these cases we have given a course of aminopterin initially, and have repeated it when it became obvious that the patient was relapsing. American workers have continued treatment with smaller maintenance doses when the patient is in remission (Farber, 1949; Dameshek, 1949).

There appears to be no certain guide to the amount of aminopterin required to induce a remission; each case has to be regarded as a therapeutic experiment. With children, a total dose of 5–10 mg. seems to be the maximum tolerated. Acting upon the belief that it is therapeutically important to give the maximum possible dose in a relatively short time, we have persisted with treatment until signs of toxicity have developed. The most important of these have been stomatitis with buccal ulceration, purpura, an increased tendency to bleed, diarrhoea, and leucopenia. Vomiting and alopecia have also been noted. In only two of the children did there seem reason for serious anxiety on this score, but both recovered and experienced remissions thereafter (Cases 5 and 12). Our experience with adults is very limited, but the two cases which remitted received 15 and 20 mg. of aminopterin in daily doses of 1–2 mg. Whether larger doses are advisable is uncertain.

We have attempted to counter the toxic effects of aminopterin by the administration of antibiotics, blood transfusions when indicated, and by withdrawal of the drug. Crude liver extract, folic acid, and vitamin B_{12} have been used, and seem to be ineffective (Farber, 1949; Dameshek, 1949).

Discussion

The principle of biological antagonism is now well established, and it has been shown that substances with the same basic structure as normal essential cellular metabolites may enter into combination with specific enzymes or other cellular proteins and cause a block in the normal metabolic pathways (Woolley, 1947). For instance, in the case of a metabolite essential for bacterial growth, Fildes and Rydon (1947) have shown that the substitution of groups distinct from the combining groups may be enough to convert a growth factor into an inhibitor.

Pteroylglutamic acid is a growth factor of wide biological importance, and in particular it seems to be essential for normal haemopoiesis (see Thiersch and Philips (1949) for literature). The 4-amino compound (aminopterin) acts, however, as an antagonist to pteroylglutamic acid, but the exact way in which this is brought about is obscure. In the case of *Lactobacillus casei* it may be the synthesis of purines and thymine which is interfered with by aminopterin (Rogers and Shive, 1948); and Stokstad *et al.* (1948), working with *Streptococcus faecalis R*, have obtained evidence of interference by methyl-folic acid of purine and pyrimidine synthesis. However, these effects may not be wholly due to simple antagonism; for instance, aminopterin inhibits the growth of chick embryos, but large doses of pteroylglutamic acid do not overcome this (Karnofsky, Patterson, and Ridgway, 1949), and pteroylglutamic acid similarly fails to neutralize the inhibitory effect of aminopterin on the growth of *Lactobacillus leishmannii* (Stokstad *et al.*, 1949).

As quoted in the introduction to this paper, there is evidence that aminopterin is capable of causing remissions in human acute or subacute leukaemia, particularly in childhood, and our own small series has yielded similar results.

Role of Blood Transfusions

The possible effect of blood transfusions in relation to remissions must be considered. In this series, with the possible exception of Case 1, it seems unlikely that the transfusions that have been given have done more than replace red cells and haemoglobin. The volumes of blood transfused were relatively small, and one patient who had a comparatively prolonged remission (Case 4) was not transfused at all. Similarly, the likelihood that all the remissions were spontaneous cannot be seriously entertained: their incidence in this, and other reported series, is too high and their relation to therapy too close to be coincidental.

The exact incidence of spontaneous remission in acute leukaemia is unknown, but Farber (1949) quotes Diamond as having found a 10% rate of spontaneous remissions in a study of 300 cases in childhood, with an average duration of under 10 weeks. Second remissions were observed in only two of the 300 cases. A few authenticated instances of apparently spontaneous prolonged haematological and clinical remissions have been reported, the longest being 21 months. Most of these were in cases of monocytic leukaemia (Whitby and Christie, 1935; Birge, Jenks, and Davis, 1949). The latter authors collected records of 11 such cases reported between 1931 and 1949.

Effect on Leukaemic Cells

In the case of the acute leukaemias which respond to aminopterin it is evidently the primitive undifferentiated cell types which are affected. Such cells rapidly diminish in numbers in the bone marrow and peripheral blood during the administration of the drug. There is also, as the result of treatment, a profound fall in the numbers of mature granulocytes in the peripheral blood, presumably due to the destruction of their more primitive precursors. Normal lymphopoiesis does not seem to be so easily affected (Berman *et al.*, 1949), but leukaemic lymphoblasts are undoubtedly susceptible (Dameshek, 1949). Thiersch (1949) has investigated the bone-marrow effects of aminopterin in man.

In those cases which respond favourably to aminopterin there is, in addition to a spontaneous rise in red cell and platelet counts, a rise in the total white cell count to approximately normal levels, the majority or all of the cells being normal adult forms. At this stage the marrow may seem to be almost normal, with active erythropoiesis and leucopoiesis. In our series, however, blast cells resembling the leukaemic cells previously present never completely disappeared.

It is impossible to say by looking at marrow smears whether aminopterin destroys the primitive cells by causing an absolute deficiency of folic acid or by a more general cytotoxic action. Farber (1949) has noted hypersegmentation of neutrophils in the blood and megaloblasts in the marrow, and we have seen the development of megaloblast-like cells in two cases following treatment. In two others, however, "megaloblasts" were present in the marrow before aminopterin was given.

The regeneration of all normal marrow elements after successful therapy seems to indicate a return to normal haemopoiesis. It is uncertain whether the subsequent reaccumulation of leukaemic cells, which apparently seems to be inevitable, is due to proliferation of residual unaffected leukaemic cells or to previously normal precursors becoming leukaemic. In practice it seems impossible to destroy all the leukaemic tissue without destroying the whole marrow and causing the death of the patient (see Case 3).

Subsequent Relapses

It is most disappointing to observe in patients who have once responded favourably that subsequent attempts at treatment are less successful and may completely fail. The leukaemic tissue appears to become more and more resistant. This acquired resistance does not seem to be a general one, for the patient appears to develop signs and symptoms of general toxic effects quite as readily in subsequent courses as when the drug is given for the first time. It is possible that continuous therapy with small doses of aminopterin will prove to be more satisfactory than the intermittent dosages we have used (Dameshek, 1949), and it is conceivable also that the substitution of another anti-folic-acid compound for the preparation originally used might prove to be a worth-while procedure. The cause of this acquired resistance is obscure. Rather similar problems exist in connexion with the chemotherapy or radiotherapy of malignant disease in general. Possibly in the case of leukaemia and aminopterin the leukaemic cells develop alternative metabolic pathways to the ones blocked by aminopterin, or it may well be due simply to persistence and proliferation of a strain of cells originally resistant.

Toxic Effects

As is seen, the toxic effects of aminopterin (or similar compounds*) are serious, and it does not seem likely that remissions can be initiated unless doses big enough to cause some toxic effects are given. The therapeutic margin, in fact, appears to be extremely small. The effects on mucous membranes causing stomatitis and diarrhoea with intestinal

*Aminopterin seems to be the most potent of the folic-acid antagonists so far employed. The other compounds used, such as a-methopterin and amino-an-fol, seem to be equally toxic if employed in doses large enough to be effective (Farber, 1949). A-ninopterin may, however, prove to be relatively slightly less toxic than aminopterin (Dameshek, 1949).

ulceration are among the most obvious toxic signs, and their development, presumably due to interference with the growth of the lining epithelial cells, is an indication to withhold the drug. Haemorrhage is a special and serious problem and repeated blood transfusions may be necessary, but may prove ineffective. The cause of the bleeding is obscure; it has been claimed in thrombocytopenic purpura and in untreated leukaemia that the amount of heparin-like substances in the blood is increased (Allen, Bogardus, Jacobson, and Spurr, 1947). Whether additional changes occur as the result of giving aminopterin, other than the depression of platelet numbers, is uncertain.

Indications and Limitations

In view of the temporary nature of the remissions and the ultimately disappointing results of the use of folic-acid antagonists in human acute leukaemia, and of the very small therapeutic margin and extreme toxicity of the drugs, it may well be asked what, if any, should be the role of aminopterin or allied compounds in the treatment of acute leukaemia. Although our experience is small it has been large enough for initial enthusiasm to be tempered and for us to realize the serious limitations of our attempts at treatment. It is impossible to be enthusiastic; the hopes of patients, parents, and doctors are raised only to be dashed by later experience.

Nevertheless, that remission can be observed at all is remarkable, and it seems difficult to withhold the drugs, should they be available, just because relapse will inevitably follow remission, any more than transfusions can be withheld just because they also are temporary expedients. It is always possible, if improbable, that a particular patient may have a prolonged and really worth-while remission, and further experience and different schemes of dosages may produce better results.

Summary

The results of treatment of 13 cases of acute and subacute leukaemia in children and adults with the folic-acid antagonist aminopterin are reported.

Clinical and haematological remissions were obtained in all of seven children treated, and in two of six adults. In those cases which responded there was a clinical return to normality and the peripheral blood was rendered normal, or almost normal, for varying periods. Although striking improvements were obtained in the bone marrows, leukaemic cells were never completely eradicated from them.

All patients who originally benefited have relapsed, and have eventually died after becoming more or less refractory to treatment.

The action of aminopterin in any given case is unpredictable and the toxic effects of the drug are severe. Great caution is necessary in its use.

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EXTERNAL ILIAC ARTERY THROMBOSIS

BY

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[WITH PHOTOGRAVURE PLATE]

On attendance at the neurovascular clinic at the Manchester Royal Infirmary, patients with the symptoms of intermittent claudication undergo a routine clinical examination which enables the underlying vascular disease to be assessed (Boyd *et al.*, 1949). In several cases the examination failed to reveal any underlying pathological condition. Subsequent investigation showed that in two cases the lesion was a unilateral thrombosis of the external iliac artery. As a search of the literature has not produced any description of such a lesion and its sequelae, a detailed account of these two cases is given. No discussion is made of other and now well-recognized causes of "proximal" arterial block such as the aortic bifurcation syndrome (Leriche and Morel, 1948).

Case 1

Whilst felling a tree on December 15, 1947, a man aged 28 was struck across the lower part of the abdomen and thigh by a large branch, causing extensive bruising. Subsequent *x*-ray examination did not show any bony injury. The accident occurred at 10 a.m., and at 1 p.m. his right foot felt numb and colder than the left. The sensation spread upwards to the knee within the next hour, but after about twelve hours it gradually receded. The patient noticed no weakness or colour change in the right leg. After ten days in hospital the contusions resolved and he was discharged.

When he resumed his ordinary activities he found that on walking about 100 yards (91 metres) a deep sickening ache was felt in the right calf and, to a less degree, in the right thigh: this disappeared after a short rest. He noticed nothing else abnormal apart from a vague sense of weakness in the leg; his general health was excellent and he continued to work as a market gardener. Because of the pain in the leg he attended the local hospital as an out-patient and was given an extensive course of short-wave diathermy and massage—without relief. He was referred to the neurovascular clinic on February 1, 1949.

The patient's general condition was that of a healthy young man; nothing abnormal was detected on systemic examination; the blood pressure was 150/90 mm. Hg. On inspection the legs

appeared normal; measurement showed slight wasting of the right thigh, the mid-thigh circumference being 17½ in. (44.5 cm.) on the right and 18¾ in. (47.6 cm.) on the left. Oscillometer readings were normal on the left leg but much reduced on the right; the arterial pulses were palpable in the left leg, but though the common iliac and femoral arterial pulses could be detected on the right side the popliteal and tibial could not. The temperature was the same in both feet.

An exercise-tolerance test was carried out on the "claudicometer"—a motor-driven moving platform fitted with an automatic recorder measuring the speed of walking and the distance traversed. The patient walked at 2½ miles (4 km.) an hour; he first felt pain in the right calf and thigh at 120 yards (110 metres) and he halted at 300 yards (274 metres). On examination immediately afterwards the right foot was paler than the left; no pulsations or oscillations were detectable in the right leg, but those in the left leg were increased from the resting level. Decrease in oscillations after exercise—the "inverse reaction"—has been demonstrated to occur below a main arterial block (Ejrup, 1948).

From the accumulated evidence the diagnosis of a traumatic thrombosis of the right external iliac artery was made.

Operation.—On February 4, 1949, an arteriectomy was performed. The right external iliac artery, which was about 3 mm. in diameter, was found to be thrombosed from the division of the common iliac artery to the level of Poupart's ligament. The thrombosed segment was removed; it dissected freely from its bed without any evident periarteritis. There were no signs of thrombosis in the right internal iliac artery, which appeared to be larger than normal. Neither the internal nor the external iliac vein was affected. A right lumbar sympathectomy was then carried out, the first three lumbar ganglia and the intervening chain being removed.

Histology.—The histological report on the resected segment of artery was as follows: "The artery is considerably smaller than normal. The internal and external elastic lamellae are abnormally folded. The lumen is filled with incompletely organized thrombus. There is no evidence of active arteritis, periarteritis, or arteriosclerosis."

Post-operative Review.—After a period of uneventful convalescence the patient returned to work. His progress was reviewed on February 5, 1950, twelve months after the operation. The patient said he was able to walk as far as he wished—on one occasion 15 miles (24 km.)—with no discomfort beyond, rarely, the mildest of aches in the right calf. On an exercise-tolerance test he walked at 4 miles (6.4 km.) an hour for a distance of one mile (1.6 km.). A slight paling of the right foot was seen after the test. Table I gives a summary

TABLE I

	Right		Left	
	At Rest	After Exercise	At Rest	After Exercise
Pulses:				
Femoral	+	+	+++	+++
Popliteal	−	+	++	++
Dorsalis pedis ..	−	+	+	++
Posterior tibial ..	−	+	+	++
Oscillations (scale divisions):				
Thigh	1	1	8	9
Calf	3	1	6	7
Supramalleolar ..	1½	−	4	5

of the observations made on the arterial pulses and oscillations at rest and after exercise. These observations are indicative of an established collateral circulation, the apparent discrepancy of the oscillometer readings being due to the phase relationship of the pulse waves.

Case 2

This patient, a man aged 23, gave no history of any definite traumatic incident, but explained that his hobby was sprint cycling. In August, 1944, after walking a distance estimated at less than 100 yards (91 metres), his left thigh and calf developed an ache, which quickly passed off when he rested. He did not remember there being any coldness or numbness in the left leg or foot. He had found also at this time that when he was cycling the left leg quickly tired and the right leg was forced to do most of the effort of pedalling. The claudication onset distance had gradually increased, and when he was referred to the neurovascular clinic on April 14, 1949, he suffered discomfort only when he walked at a fast pace or during a cycle race, the factor which had caused him to seek medical advice. There was no relevant previous medical history.

On general examination nothing abnormal was detected; the blood pressure was 130/80 mm. Hg. The nutrition of

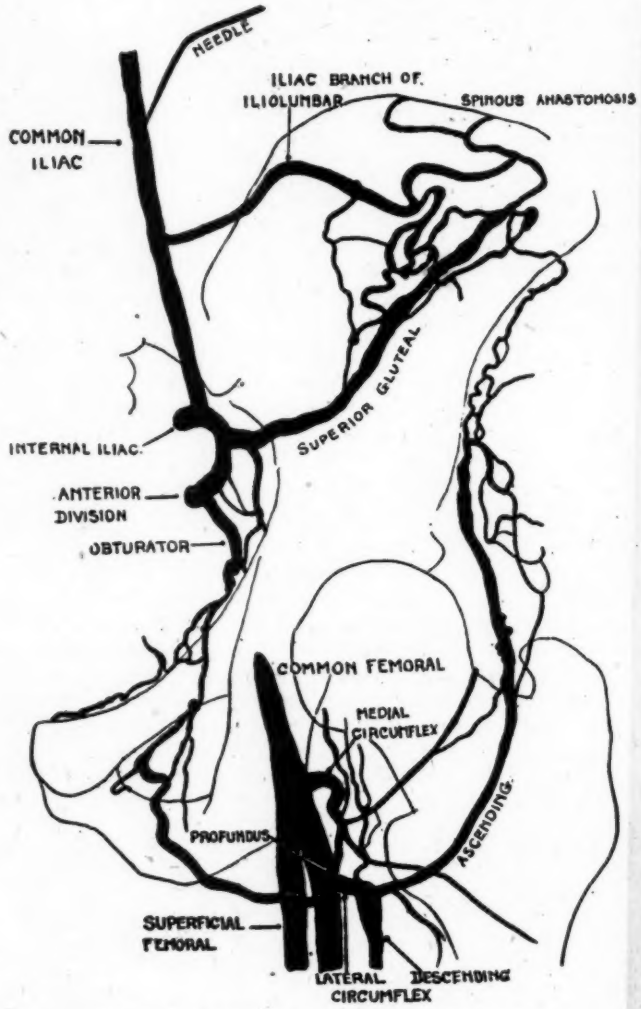

FIG. A.—Diagrammatic arteriogram of Case 2.

the legs was excellent, but there was slight wasting of the left leg, the thigh being ¾ in. (1.9 cm.) and the calf 1 in. (2.5 cm.) less in circumference than on the right side. Oscillometer readings were normal on the right leg but reduced on the left; the arterial pulses were palpable on both legs; the femoral pulse, however, was less marked on the left side.

On the exercise-tolerance test the patient walked at 3 miles (4.8 km.) an hour for a distance of one mile (1.6 km.), at which point he complained of a feeling of discomfort in the left thigh. The left foot was seen to be slightly paler than the right. Oscillometer readings were increased on the right leg and still further reduced on the left side; the arterial pulses were scarcely palpable on the left side. A left external iliac artery thrombosis was diagnosed.

Operation.—An arteriectomy was performed on April 19, 1949. A thrombus was found extending from the division

of the left common iliac artery to a point ½ in. (1.25 cm.) below Poupart's ligament, thus involving the whole of the external iliac and upper part of the common femoral arteries. The internal iliac, external pudental, superficial epigastric, and external circumflex iliac arteries on the left side were hypertrophied but otherwise appeared normal. An arteriogram taken after the injection of 10 ml. of thorotrast into the common iliac artery showed the excellence of the collateral circulation (Fig. A). The thrombosed segment dissected free without difficulty—there being no periarterial reaction—and was excised.

A left lumbar sympathectomy was also undertaken, the first three lumbar ganglia and intervening chain being removed.

Histology.—The histological report on the excised segment of artery read as follows: "The artery is much decreased in size, and in consequence the internal and external elastic lamellae are tortuous and thickened. There is a slight increase in the amount of medial elastic tissue. The lumen is filled with fibrous tissue which has incorporated the intima. In this fibrous tissue are a few blood spaces which are lined by a simple epithelium. There is no evidence of any inflammatory reaction. There is nothing to suggest the cause for this now quiescent thrombosis" (Plate, Figs. 1, 2, and 3).

Post-operative Review.—A review of the patient's condition was made four months after operation, and the original tests were repeated. The intervening period was too short for the final results of the operation to be assessed. On the exercise-tolerance test the patient walked at 3 miles an hour for a distance of one mile without discomfort. The left foot did not appear pale. The observations are summarized in Table II.

TABLE II

	Left	
	At Rest	After Exercise
Pulses:		
Femoral	+	+
Popliteal	+	+
Dorsalis pedis	++	++
Posterior tibial	+	++
Oscillations (scale divisions):		
Thigh	1	<½
Calf	4	1
Supramalleolar	2	<½

Literature

The occurrence of intermittent claudication with no evidence of arterial disease has been thought to be due to arterial spasm. Simmons (1936) states: "A proportion of cases of intermittent claudication are due to pure spasm of the arteries in neuropathic individuals, and no structural disease of the vessels is demonstrable either at the time or in later years." Such cases have also been described under the term "paradoxical spasm."

Pearl (1937) reported six cases under the heading of "angiospastic claudication." When these patients took exercise the foot on the affected side became pale and the dorsalis pedis pulse ceased to be palpable. These phenomena did not occur after a lumbar sympathetic block with procaine; this fact was regarded as evidence of arterial spasm.

The possible existence of a high arterial block does not seem to have been considered by these authors, and in consequence their cases were not investigated from this point of view.

A case of "spastic claudication" was described by Lindqvist (1945a). Further investigation showed this to be due to "an organic constriction of the lower part of the aorta" (Lindqvist, 1945b).

Some doubt is felt with regard to the existence of "angiospastic claudication" as a separate entity. Diagnosis of such a condition is considered unjustifiable until a block proximal to the femoral artery has been excluded.

Clinical Features

The presenting symptom in both of our cases was intermittent claudication. During exercise the patients noticed vague discomfort in the calf and thigh followed by typical claudication pain, relieved by a short rest. The degree of claudication, as usual, depended on the balance between blood supply and demand, becoming less severe as the collateral circulation developed.

The arterial pulses of the limb were diminished, though not to the same degree in the two patients. In Case 1 only the femoral pulse was present; in Case 2, with less severe claudication, all the pulses were present but the femoral pulse was diminished. After exercise the arterial pulses of the affected limb disappeared completely in Case 1 and almost completely in Case 2.

Oscillometric readings were taken while the patients were resting. In comparison with those of the normal side the readings on the side of the lesion were much reduced in Case 1 and moderately so in Case 2. After the patients had walked a sufficient distance to produce the claudication pain it was found that the oscillometric readings were increased on the normal leg and still further reduced on the painful leg. The foot on the painful side also became paler.

Other investigations revealed no significant changes. Temperature gradients and electrical skin-resistance readings were normal; straight radiographs of the abdomen, pelvis, and limbs showed no vascular calcification; the clotting time and platelet counts were within normal limits.

The diagnostic features which must be emphasized are the disappearance or marked diminution of pulses and oscillometric readings after exercise—Ejrup's (1948) "inverse reaction"—followed by a rapid return to normal on resting.

Possible Causes of the Arterial Thrombosis

Arterial Disease

Segmental thrombosis of a main vessel in young men is generally regarded as due to "thrombo-angiitis obliterans." The onset of this condition is usually acral, and a history of phlebitis is common. In older subjects thrombosis of a main vessel is a frequent complication of arteriosclerosis. Of the patients with this condition seen in our clinic approximately 50% have a thrombosis of one or both popliteal arteries and 10% of one or both femoral arteries. The histological findings and the lack of progression in the case histories quoted is thought to exclude either of these diseases.

Idiopathic Thrombosis

Nygaard and Brown (1937) have described five cases with "non-reactive" thrombosis of the main limb vessels under the term "essential thrombophilia." In addition to the limb vessels there was more widespread arterial thrombosis in the cerebral, renal, and coronary vessels; a deep or superficial venous thrombosis was also found. Four cases showed an increase in the coagulability of the plasma.

Examples of a "bland arterial thrombosis" have been reported by Leriche and Stricker (1933) under the heading of "spontaneous localized monarteritis of indeterminate origin." Learmonth, Blackwood, and Richards (1944) have described a similar condition by the term "localized arterial thrombosis of indeterminate origin."

Trauma

Arterial thrombosis is sometimes seen in healthy arteries after severe injury—" run-over " accidents or heavy objects falling across the limb. The accompanying vein is usually thrombosed ; fractures are common. An extensive diffuse arterial haematoma, resulting in a tense swelling of the limb and distal ischaemia, is often encountered. Thrombosis of a healthy artery by recurrent crutch pressure has been reported by Platt (1930). Vessels already damaged by arteriosclerosis may be thrombosed by a lesser degree of trauma.

The most common cause of arterial damage resulting in thrombosis is indirect trauma. The site is either where the artery is in close relation to a joint or where it lies between bone and the tendinous insertion of a muscle—for example, the popliteal artery where it enters the popliteal tunnel at the level of the upper border of the femoral condyle, or the subclavian artery as it lies on the first rib behind the tendon of the scalenus anticus. The pathology of the lesion is not clear, but contusion of the arterial wall causing rupture of the vasa vasorum and an intramural haematoma is a possibility. A similar lesion or an intimal tear may be due to a " stretch-strain " or may be the result of traction on a muscular branch.

The popliteal artery is the most common site of thrombosis due to indirect trauma. Boyd and Wilde (1950) have shown that this artery is firmly fixed to the oblique ligament of the knee-joint. The artery enters a fibromuscular canal at the level of the upper border of the femoral condyles, emerging 2 cm. below the knee-joint. During its passage through the " tunnel " the artery may be damaged by contraction of the surrounding muscles or by stretching from the attachment to the oblique ligament on repeated flexion of the knee—especially when fixed to the " tunnel " walls through inflammatory changes in the accompanying vein or lymphatic vessel. Stretch-strain of the artery at the level of the upper border of the femoral condyles occurs with sprains of the knee-joint of the type producing internal derangement. Arteriograms show that the prethrombotic lesion is always at this level, where the artery enters the popliteal canal.

The external iliac artery has been shown to be fixed to the ilio-psoas muscle at the level of Poupart's ligament by the fusion of the iliac and transversalis fascia with the adventitia of the artery (Panton, 1923).

The causes of the thrombosis in the above two cases would seem to be direct trauma in Case 1, who was struck by the falling tree, and indirect trauma due to stretch-strain from repeated flexion of the hip-joint in Case 2, the sprint cyclist.

Treatment

The important collateral circulation after the occlusion of the external iliac artery is by way of the gluteal and obturator arteries and the spinous and cruciate anastomoses. The afferent vessels to these anastomoses arise from the internal iliac and occasionally the common iliac arteries, and receive sympathetic innervation from the lumbar sympathetic chain through the somatic nerve bundles. The common iliac artery is also innervated from the presacral plexus. A lumbar sympathectomy therefore denervates not only the limb vascular bed but also the main collateral vessels.

The incision for the lumbar sympathetic chain is made as small as possible in order to avoid excessive damage to the loin collateral vessels. It is also made a little lower than the standard extraperitoneal loin incision so that the iliac vessels may be more easily exposed. More bleeding than usual is experienced during the muscle section, and careful haemostasis must be secured. The lumbar chain from L1 to L3 is removed, and the diaphragmatic crus is split to ensure section of the highest lumbar ganglion. Only by the removal of L1 ganglion can the necessary high thigh denervation be obtained (Ratcliffe and Jepson, 1950).

In each of the cases quoted a segment of thrombosed external iliac artery was removed. This was done primarily for histological verification, but there is also reason to believe that removal of the thrombotic zone may discourage further spread. Leriche has suggested that the thrombosed artery initiates reflex vasospasm, and hence should, for this reason alone, be excised.

Prognosis

In both cases, at the post-operative review, exercise caused the limb pulses to become palpably stronger, whereas pre-operatively the converse had been observed.

Subjectively, both patients considered their condition to be much improved. The follow-up period cannot, however, be taken as sufficient for judgment of the long-term results.

If the analogy between primary popliteal thrombosis and these cases is just, it may be assumed that the prognosis is excellent. With increasing age, however, the effect of arteriosclerosis may be more severe in the leg in which the circulation is already impaired by the occlusion of the main artery.

Summary

Two cases of thrombosis of the external iliac artery are reported.

The syndrome of a " high arterial block," as illustrated by these cases, is described. Stress is laid on the " inverse reaction " of the oscillometric readings following exercise.

The possible aetiology of the condition is discussed and reasons for a traumatic origin are given.

Lumbar sympathectomy was performed on these cases and details of the post-operative improvement are given.

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A scholarship of £100 to £150 will be awarded by the National Association for the Prevention of Tuberculosis to a registered female nurse, working at the time of her application in Scotland, whose name is on the Queen's Roll of the Queen's Institute of District Nursing. Preference will be given to a nurse working in the Highlands. The scholarship will enable her to spend a period of from three to six months in post-graduate study in hospitals or clinics in Scotland, England, or Scandinavia. Candidates should state age, qualifications, and previous experience ; reasons for wishing to do postgraduate work in tuberculosis ; and should affirm their intention to continue in tuberculosis work after attaining the scholarship. Application should be made to Miss A. J. Weir, Scottish Secretary, N.A.P.T., 65, Castle Street, Edinburgh, 2, by November 1.

CEREBROSPINAL FLUID IN 302 CASES OF INTRACRANIAL TUMOUR, ABSCESS, AND SUBDURAL HAEMATOMA

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Intracranial tumours differ greatly as regards the possibility of diagnosis from the clinical history and examination alone, without the aid of ancillary investigations. There is rarely any difficulty in cases with the classical triad of progressive history, focal manifestations, and increased intracranial pressure. The various types of tumour behave differently, however, in their effects on the brain and on intracranial pressure, depending on their pathology, rate and manner of growth, and situation. Thus there may be no focal manifestations to reveal the position of a tumour, the presence of which is virtually certain from signs of high intracranial pressure, or, on the other hand, there may be no increase of intracranial pressure to suggest tumour as the cause of a focal disturbance; also, a detailed history, which is so important, may not be available. Again, some tumours produce only general manifestations such as fits, dizziness, or headaches, which are often due to other neurological conditions or to general medical causes. In many cases, therefore, clinical examination must be supplemented by ancillary tests, the choice of which should depend upon the nature of the desired information and upon full appreciation of their value and limitations.

Points in Diagnosis

Ancillary methods of diagnosis should always be used with discrimination, never as a routine, and only when diagnosis remains uncertain or requires amplification to guide treatment; they are not to be regarded as short cuts to diagnosis, replacing careful clinical examination. Simple, easily performed tests like lumbar puncture are apt to be used unnecessarily, without regard to whether they are likely to be helpful, especially when the clinical examination is not as thorough as it might be. Moreover, belief in the necessity for lumbar puncture is naturally influenced by the clinician's neurological experience and the type of clinical material—that is, whether the test is used merely to amplify the diagnosis of tumour or is used in the hope of excluding tumour or of obtaining positive evidence of an organic lesion.

Neurosurgeons and physicians no doubt view diagnostic lumbar puncture for brain tumour from different standpoints, and neurosurgeons, by reason of their greater experience of tumours and simulating conditions, should use it less than physicians. It is of interest to recall that in Cushing's clinic lumbar puncture was never used for diagnostic purposes—a policy which he soon adopted after the occurrence of fatalities attributable to the test (which still occur) and because the additional information obtained was negligible. The belief that lumbar puncture is of little value to neurosurgeons does not apply, however, to its proper use by clinicians who only occasionally encounter cerebral tumours.

Lumbar puncture, as opposed to visualizing procedures like ventriculography or arteriography, yields numerical results which, alone, do not provide specific evidence of tumour, and only rarely do so when considered along with the clinical findings. Moreover, although usually regarded as a safe procedure, lumbar puncture is potentially dangerous in cases with high intracranial pressure and can be fatal, and there is always the slight risk of meningitis. It is therefore important, for the proper and safe use of the test, to assess its value and its limitations in tumour cases by determining how useful it may be (*a*) as a general or specific test of tumours, and (*b*) in the management of known tumour cases, either as a means of foretelling the pathology and operability of the tumour or as a possible substitute for more complicated and dangerous methods of investigation, such as ventriculography.

The literature concerning diagnostic lumbar puncture for brain tumour is scanty, and has perhaps given a false impression of the frequency of what may be regarded as the complete fluid syndrome—namely, raised pressure, increased protein, and sometimes xanthochromia and moderate pleocytosis. It was evident from the earlier studies of small groups of cases that there is no constant C.S.F. picture characteristic of brain tumours, nor, because of their great variety in type and situation, would it be expected. Later analyses of larger series, with special attention to the situation and pathological type of the growth, again showed that spinal fluid examination is rarely conclusive in the differential diagnosis of tumour from other diseases of the brain; and that one-third or more of tumour cases have normal fluid, while an abnormal fluid is not by itself diagnostic of tumour. It was shown, however, that tumours of certain types or in certain situations commonly have either normal or abnormal fluids as the case may be (Greenfield and Carmichael, 1925; Hare, 1935; Merritt and Fremont-Smith, 1937). The fact that the spinal fluid is often normal detracts from the value of the test, but the discovery of abnormal fluid as the sole evidence of organic disease, when symptoms have been attributed to conditions such as neurosis or idiopathic epilepsy, is important. We have endeavoured to go a stage further by assessing the fluid findings in relation to the more common clinical syndromes and difficulties which confront the neurosurgeon, and to estimate their value to the general physician in preliminary diagnosis.

The diagnosis of intracranial tumour requires answers to three questions: (1) Is a tumour present? (2) Where is it? (3) What kind is it? Patients may be divided into three categories depending on how far these questions can be answered from the clinical findings alone.

1. *Suspected or Probable Intracranial Tumour.*—Progressive symptoms suggest the possibility of tumour, but there is no papilloedema. It is in the general investigation of this large group of patients that lumbar puncture could be of great value in verifying or excluding tumour.

2. *Unlocated Intracranial Tumour.*—Signs of increased intracranial pressure reveal almost certainly the presence of a tumour or other space-occupying lesion, but there are no focal manifestations to indicate its position. An appropriate diagnostic method such as ventriculography is usually required to locate it as lumbar puncture does not help.

3. The symptoms and signs are so characteristic that clinical (and *x*-ray) examination by itself provides definite evidence not only of the presence of a tumour but also of its situation, and sometimes also its pathology—for example, some cases of tumour involving the optic chiasm, meningioma, brain-stem glioma, and metastatic tumour. Lumbar puncture is unnecessary, and treatment can be decided without further investigation. Sometimes, however, additional information regarding pathology—for example, whether the tumour is a glioma or a meningioma—would be helpful in surgical management if

it could be obtained easily, but, as will be seen, the cerebrospinal fluid rarely helps in this respect.

With these clinical categories and problems in mind we have analysed the C.S.F. findings in 302 consecutive cases of histologically verified intracranial tumour, abscess, and subdural haematoma which were seen by us at the National Hospital, Queen Square, London, during two and a half years (1935–8). Many patients did not have operation, and there were 145 necropsies. All tumours were examined histologically by Dr. J. G. Greenfield. This report was delayed by the war, but further experience has confirmed our conclusions, with certain additions that will be mentioned.

The lumbar spinal fluid was obtained in 286 cases and the ventricular fluid in 128. All fluid examinations were made by Dr. J. G. Greenfield or Dr. J. N. Cumings. Our analysis concerned protein content and cell count, the only constituents affected by tumours. The protein was measured by Mestrezat's diaphanometric method, and up to 60 mg. per 100 ml. in the lumbar fluid and 10 mg. per 100 ml. in the ventricular fluid were regarded as normal. A cell count of less than five cells per c.mm. was taken as normal.

In Table I the total protein values in all cases are given in order to convey a clearer impression of the relative ranges of figures than would be presented by any arbitrary grouping into degrees of abnormality.

TABLE I.—*Lumbar C.S.F. Protein with Intracranial Tumours*

Type and Situation of Tumour	Total Protein in Lumbar C.S.F. (mg. per 100 ml.)	
	Normal	Increased
Gliomas (125 *cases*)		
Astrocytomas:		
Cerebral	25, 25, 30, 30, 30, 35, 35, 35, 40, 45, 45, 45, 55, 55, 55	65, 70, 70, 80, 80, 80, 100, 110, 125, 150, 440
Corpus callosum	30, 40, 40	70
Thalamus, midbrain	30, 30, 30, 50	70, 80, 90, 90, 120, 140, 150
Cerebellar—adults	45, 45, 50, 60	70, 150
" children	40, 40, 45	70, 80, 90, 140
Intraventricular	55	
Glioblastomas:		
Cerebral	20, 25, 30, 40, 40, 40, 45, 50, 50, 50, 55, 60, 60, 60, 60	65, 65, 70, 75, 90, 90, 100, 100, 100, 120, 120, 130, 150, 180, 220, 240, 320, 400, 800, 1,280
Corpus callosum		190, 220, 260, 300, 400
Thalamus, midbrain		110, 120, 160
Oligodendrogliomas	35, 40, 40, 40, 50	65, 80, 85, 90, 110, 120, 160, 200
Medulloblastomas	45, 60	80, 90, 190
Ependymomas	60	70
Gliomas pontis	30, 40, 50, 55, 60	70
Glioma of infundibulum		240
Meningiomas (62 *Cases*)		
Cerebral convexity	30, 40	65, 70, 90, 90, 90, 125, 130, 140, 160, 160, 175, 175, 180, 220, 240, 280
Parasagittal	40, 40, 45, 50, 60	90, 100, 125, 130, 170, 350, 360
Olfactory groove		120, 180, 220, 300
Tuberculum sellae	40, 60	80, 90, 90, 100, 120, 120, 160
Sphenoid ridge	55	80, 100, 140, 175, 190, 200, 220, 300, 450
Middle fossa	60	95, 120
Posterior fossa		70, 100, 130, 140, 220
Intraventricular		120
Neurofibromas (16 *Cases*)		
Acoustic		100, 180, 180, 220, 350, 360, 400, 440, 640, 720, 750, 880, 900
Trigeminal		380
Multiple		240, 280
Pituitary Tumours (36 *Cases*)		
Chromophobe adenomas	35, 50, 55	70, 70, 75, 80, 90, 90, 100, 100, 100, 120, 130, 150, 150, 180, 180, 680, 760
Acidophil adenomas	30, 40	80, 110, 180, 190
Craniopharyngiomas	20, 35, 40, 50	75, 80, 80, 90, 100, 140
Miscellaneous Groups (37 *Cases*)		
Metastatic	30, 55	75, 80, 100, 120, 150, 560
Haemangiomas:		
Cerebellar	45	80, 90, 220, 480
Parietal	25	70
Angiomas	60	140
Sarcoma—cerebral	60	180
" cerebellar	20, 40, 50	
Colloid cyst—III vent.	35, 55	
Dermoid—III vent.		320
Pinealoma		175
Epidermoid—petrous		75
" parasellar	60	
Chordoma of sphenoid		160
Tuberculoma (multiple)	60	
Subdural haematoma	45, 45, 50, 50, 60	80, 90

Lumbar Fluid

Tumours

Astrocytomas.—The protein figures were rather low, and more than half were normal. In only one instance were the cells increased (8 cells). The protein values did not seem to be influenced by the situation of the tumour, by its character, whether cystic, solid, or calcified, or by its proximity to the ventricles.

Glioblastomas.—These had a much wider range of protein figures than the astrocytomas; they were sometimes very high, but were often normal. In 13 cases (30%) there was a considerable increase of cells (14 to 70) and the fluid was usually deep yellow or orange. Pleocytosis with xanthochromia in known tumour cases was characteristic of glioblastoma; it occurred with all glioblastomas of the corpus callosum. Post-mortem examinations showed that the ventricular walls were extensively infiltrated in all cases with increased cells, but not in those without pleocytosis, even though there was marked increase of protein. The type of cell varied, but it is of interest that the percentage of polymorphs in two cases was as high as 32 and 84 respectively. The cases with moderately raised protein usually had colourless fluid without increase of cells: the thalamus and midbrain glioblastomas were in this category.

The rarer types of glioma showed no distinguishing features. One case of medulloblastoma had 9 lymphocytes.

Meningiomas.—The protein was more often increased with meningiomas than with gliomas and frequently was very high, but it was sometimes normal. In 7 instances the fluid was faintly yellow, but never so deeply coloured as with some glioblastomas. Among 62 cases pleocytosis occurred in only 2, each with 8 cells. There was no difference between meningiomas over the convexity of the cerebral hemisphere and those on the skull base, both having a wide range of figures; nor was there any relationship to the age of the patient, duration of symptoms, size or type of tumour, or intracranial pressure.

Neurofibromas.—This was the only group in which the protein in the spinal fluid was always increased; the figures were usually very high, and when above 350 mg. the fluid was slightly yellow. The cells were never increased. There was usually a moderate elevation in the middle of the Lange curve.

Pituitary Tumours.—The fluid showed no special features and there was no relationship to the consistency of the adenoma or to its position, whether intrasellar, suprasellar, or with intracranial extension. Two cases, without apparent reason, had exceptionally high protein and yellow fluid. One case of craniopharyngioma had 9 cells.

Metastatic Tumours.—All tumours were bronchogenic in origin except one from the kidney. The fluids showed a wide range of protein values, but no increase of cells. (Ten recent cases of metastatic bronchial tumours had similar protein figures, ranging from normal to 150 mg., but three of them had increased cells with 9, 14, and 85 lymphocytes.) In the case with 560 mg. of protein the meninges and ventricular walls were diffusely infiltrated with bronchogenic tumour cells without any localized

tumour formation; the lumbar fluid was straw-coloured and contained only one cell. All other fluids were colourless.

Blood-vessel Tumours.—The three cases with high protein had yellow fluid.

Pinealoma.—In this single case the fluid was colourless and contained 87 cells, including one polymorph. Two recently observed cases had 60 mg. protein with 8 lymphocytes, and 136 mg. protein with 30 lymphocytes respectively.

Tuberculoma.—Three recent cases all had increased cells—7, 10, and 75 lymphocytes with 90, 20, and 25 mg. of protein respectively.

Cerebral Atrophy.—Progressive hemiparesis, mental deterioration, fits, and other cerebral symptoms may be associated with cerebral atrophy, the diagnosis of which rests upon ventriculographic demonstration of dilated ventricles. This condition sometimes has to be considered in the differential diagnosis of brain tumours. In a number of recently observed cases the spinal fluid was usually normal but occasionally contained a slight excess of protein.

Chronic Subdural Haematomas

In this curable condition, which clinically often resembles hopeless cerebral gliomas and is apt to be missed, the protein figures were comparatively low, usually normal. In one case the fluid was straw-coloured and in another there were 8 cells.

Abscesses

The lumbar fluid was normal in 40% of this small group of abscesses. In the remainder the protein was considerably increased, and the number and type of cells varied, as shown in Table II, depending presumably upon whether

TABLE II.—*Lumbar C.S.F. Protein and Cells with Abscesses*

Situation of Abscess and Source of Infection	Total Protein (mg. %)	Cells
Frontal: Frontal sinus ..	40	2 lymphocytes
„ ?	40	0
Parietal: Carbuncle of hand ..	70	2·5 lymphocytes
„ Pulmonary	80	5 cells; 80% polymorphs
„ Osteomyelitis of arm	160	290 cells; 48% „
Temporal: Otitic	40	0
„ „	150	9 cells; 44% „
„ „	160	7 lymphocytes
Cerebellar: Otitic	35	4 „
„ „	200	9 „

the abscess was still surrounded by a zone of encephalitis or had become firmly encapsulated, and whether there had been any recent meningitis or recurrent encephalitis.

Spinal fluid examination in 15 cases of abscess recently treated in a general hospital (Leeds Infirmary), where they are probably seen earlier than in a neurological hospital, gave similar results as regards protein content, the highest figure being 80 mg., but the cells were more often considerably increased—namely, six cases had only one cell, three a slight increase of 8 to 12 cells, and six a considerable pleocytosis ranging from 22 to 300 cells; polymorphs were usually but not always present, and they were more numerous, up to 50%, with the higher counts.

A slight or even considerable increase of lymphocytes is of no value in differentiating abscesses and tumours, as it may occur with either. The presence of polymorphs, however, is strongly in favour of abscess when the fluid is colourless, because in tumour cases they are found only with glioblastomas, which can be readily distinguished by the yellow fluid.

It is of interest that the fluid findings in 7 recently observed cases of presumed acute pyogenic encephalitis, which resolved without abscess formation and with disappearance of focal signs, resembled those due to abscess: all had normal protein except one with 75 mg., while the cells varied from normal to 350, usually with a mixture of polymorphs. Thus the spinal fluid gives no indication whether an acute cerebral infection has progressed to abscess formation or will resolve.

It may be mentioned that turbid fibrinous fluid with marked increase of cells, mainly polymorphs, indicates acute meningitis, which is usually obvious clinically, but an abscess may also be present. Also, it should be emphasized that lumbar puncture is often dangerous with abscess owing to the risk of producing a pressure cone, and consequently, because of the non-specific findings, it should not be done unless absolutely necessary.

Comment on Lumbar Fluid Examinations

1. The spinal fluid findings alone are not diagnostic of intracranial tumour. Increased protein indicates an organic lesion, but not necessarily tumour, and normal protein does not exclude tumour.

2. The lumbar fluid examination taken in conjunction with clinical findings is of value in two circumstances: (i) Cerebral tumours with deep yellow fluid, high protein, and moderate pleocytosis can be identified as glioblastomas invading the ventricle. With this exception no distinction is possible between infiltrating and non-infiltrating tumours. (ii) Acoustic neurofibromas always produce high protein, and can therefore be excluded in cases of cerebello-pontine angle syndrome with normal fluid.

3. The spinal fluid is of no value in determining the situation of an unlocated tumour with papilloedema.

4. Regarding the more common clinical syndromes and difficulties, the following observations may be made:

(*a*) Of tumours that may resemble acoustic neurofibromas clinically, meningiomas in the cerebello-pontine angle had protein values of 130, 140, and 220 mg., which were similar to the lower figures for neurofibromas, while gliomas of the pons had normal protein.

(*b*) The clinically similar cerebellar tumours in childhood, astrocytomas and medulloblastomas, cannot be distinguished by lumbar puncture.

(*c*) It was sometimes difficult clinically to distinguish between cerebellar and frontal tumours; the latter included meningiomas, oligodendrogliomas, astrocytomas, and glioblastomas. The lumbar protein in these instances was normal or only slightly raised, which was also the common finding with cerebellar gliomas.

(*d*) As regards parasagittal tumours, the wide range of protein values for meningiomas (40 to 360 mg.) makes it impossible to differentiate them from gliomas, mostly astrocytomas, although the figures for gliomas were limited to between 70 and 130 mg.; so that a very high protein suggests meningioma.

(*e*) Tumours in the chiasmal region—tuberculum sellae meningiomas, pituitary adenomas, and craniopharyngiomas—cannot be differentiated. It may be emphasized that normal C.S.F. does not exclude tumour as the cause of unexplained failing vision with progressive visual field defect and perhaps optic atrophy.

(*f*) It is often impossible clinically, even with ventriculograms, to identify the pathological types of tumours in the region of the pineal and midbrain. Pinealomas may be distinguished from other tumours by excess of cells when present, but it appears from some case reports that the cell count may be normal. The protein values in four cases of midbrain astrocytoma were 50, 70, 80, and 140 mg., in two glioblastomas 120 and 160 mg., and in one ependymoma 60 mg.; in none were the cells increased.

(*g*) The C.S.F. does not help in the identification of metastatic tumours.

(*h*) A slight increase of cells from 5 to, say, 10 is of no diagnostic significance, as it occurs with most types of tumour and with abscess; but it is noteworthy that, as regards tumours, more than 10 cells were found only with glioblastomas, pinealomas, metastatic tumours, and tuberculomas. No tumour cells were identified in the fluid, but their occurrence has occasionally been reported by others in cases of medulloblastoma or metastatic tumour.

5. In the diagnosis of abscess the C.S.F. is of little value. The presence of polymorphs is suggestive, as they were not found with tumours, except some glioblastomas with xanthochromic fluid, but they may also occur with resolving pyogenic encephalitis.

6. Spinal fluid is of no value in the diagnosis of chronic subdural haematoma.

Ventricular Fluid

The cerebrospinal fluid from one or both lateral ventricles was obtained during ventriculography or operation in 128 cases, 16 of which had not previously had lumbar puncture. As ventricular fluid cannot be obtained without a surgical procedure its examination has no place in the preliminary investigation of brain tumours; moreover, analysis of the findings showed that they are of little real value in diagnosis or in the surgical management of known tumour cases.

Fluid was obtained from both ventricles in about one-half of the 74 cases in which the tumour was situated above the tentorium; in the others only one ventricle was tapped, usually on the side opposite to the tumour. The frequency of increased ventricular protein with the more common supratentorial tumours (astrocytoma, glioblastoma, and meningioma) is shown in Table III.

TABLE III.—*Ventricular C.S.F. Protein with Supratentorial Tumours*

Type of Tumour	No. of Patients	Ipsilateral Ventricle		Contralateral Ventricle	
		No. Examined	No. with Increased Protein	No. Examined	No. with Increased Protein
Astrocytoma ..	24	17	8 (47%)	23	7 (30%)
Meningioma ..	19	7	5 (71%)	19	9 (47%)
Glioblastoma ..	16	5	4 (80%)	15	8 (53%)

In most cases with posterior fossa tumours fluid was examined from only one ventricle. In the 19 instances in which both ventricles were tapped the fluids were identical whether the protein content was normal or increased; and it is assumed that this is true for all midline tumours—cerebellar, pineal, third ventricle cysts, and craniopharyngiomas.

Astrocytomas.—Fluid was examined from 37 cases. All 13 patients with cerebellar astrocytomas, mostly children, had normal ventricular fluid except three with an increased protein content up to 35 mg. (the medulloblastomas showed similar results). As regards the 24 cerebral astrocytomas, it is noteworthy that the fluid was normal in both ventricles in 9 out of 16 bilateral examinations. One case with a pedunculated 50 g. astrocytoma within one lateral ventricle had a protein content of only 5 mg. in each ventricle. The abnormal fluids rarely contained more than 50 mg. in the ventricle on the side of the tumour.

Glioblastomas.—The fluid was more often abnormal than with astrocytomas, but the protein values were similar in range; the fluid was, however, sometimes normal in both ventricles.

Meningiomas.—There was no essential difference between meningiomas and gliomas as regards frequency and degree of abnormality in the ventricular fluid. It was normal in both ventricles in only 2 out of 7 cases. In half the cases there was, as with glioblastomas, increased protein content in both ventricles.

Oligodendrogliomas.—The protein content was raised in the homolateral ventricle in 2 out of 4 cases to 20 and 50 mg. respectively, but was normal in the contralateral ventricle in all 5 cases examined. Post-mortem specimens showed that invasion of ventricular walls by these tumours produces less change in the fluid than is produced by other gliomas.

Ependymomas (Fourth Ventricle).—The protein was raised to 15–20 mg. in all 3 cases examined.

Haemangiomas.—Of the 7 cerebellar cases the ventricular fluid was normal in 5, but in the others it was raised to 60 and 180 mg. (480 mg. in the lumbar fluid) respectively.

Acoustic Neurofibromas.—Three out of 9 cases showed an increase of protein ranging from 15 to 40 mg.

Metastatic Tumours.—Two of the 3 cases examined showed normal fluids on both sides.

Other Tumours.—The fluids were normal in all 7 cases of craniopharyngioma, in 2 cases of colloid cyst of the third ventricle, and in the single case of pineal tumour.

Abscesses.—In one case of cerebellar abscess (lumbar fluid protein, 200 mg.) the ventricular protein was raised to 25 mg. The protein was slightly raised in 2 cases, but there was no increase in cells.

In the entire series there were 8 cases with exceptionally high protein content (100–1,000 mg.) in both lateral ventricles—namely, two large cerebral astrocytomas, two glioblastomas, two meningiomas, one cerebellar haemangioma, and the case of diffuse metastatic infiltration of the meninges and ventricular walls mentioned previously. The fluids were usually yellow.

Comment on Ventricular Fluid Findings

Examination of ventricular fluid from one or, when obtainable, both sides is of little value in diagnosis or in deciding treatment. With unilateral supratentorial tumours the protein in the ventricle on the side of the tumour may be normal or increased, but it may also be increased in the contralateral ventricle; moreover, the fluid may be normal in both ventricles with a tumour in one cerebral hemisphere or in the midline above the tentorium or in the posterior fossa.

Comparison of the protein content in the lumbar and ventricular fluids has been advocated as a means of localizing tumours to the posterior fossa, to the third ventricle, or to one cerebral hemisphere (Merritt, 1935). It is our opinion, however, that combined puncture has no practical value, as it does not supply sufficiently accurate information for surgical purposes; if the clinical findings are inadequate for determining the precise localization, visualizing methods such as ventriculography are necessary.

Pathogenesis of Changes in the C.S.F.

We have no observations about the origin of excessive protein and cells in the cerebrospinal fluid. The various theories regarding this have been discussed by Greenfield (1936). There are probably several mechanisms, of varying importance in individual cases—namely, transudation of protein from the surface of the tumour, liberation of protein and cells from within a degenerating tumour that has infiltrated through the ventricular wall, or drainage of protein from oedematous brain surrounding the tumour. The last mechanism is, we believe, the chief factor with convexity meningiomas, which are often associated with

marked oedema throughout the cerebral hemisphere and high spinal protein. It is unlikely that stasis of the fluid circulation, resembling that seen below spinal tumours, is an important cause of excessive protein with brain tumours or that pleocytosis is due to meningeal reaction.

Spinal Fluid Pressure

Although this investigation was concerned with the clinical value of spinal fluid examination, a few remarks may be added about lumbar C.S.F. pressure and its measurement. The borderline of abnormally high pressure is assumed to be 180 to 200 mm. of water. Undue importance is apt to be attached to the lumbar pressure as conclusive evidence for or against an intracranial expanding lesion, and, moreover, lumbar puncture to verify high pressure may be dangerous.

It must again be stressed that papilloedema makes lumbar puncture unnecessary and that even before papilloedema appears many tumours can be diagnosed on clinical grounds alone. On the other hand, high pressure may be the only objective evidence of an intracranial expanding lesion.

The importance of carefully positioning the patient is sometimes overlooked and too high a reading is obtained. The lumbar needle and the centre of the head must be on the same level, and the patient must be completely relaxed and breathing easily. It is customary to facilitate insertion of the needle by fully flexing the head, trunk, and legs. Before taking measurements, however, the neck should be straightened to avoid constriction of the jugular veins, and the thighs extended slightly to avoid compression of the abdomen. Pressure readings taken under general anaesthesia are of no value.

The danger of death from coning after withdrawal of lumbar fluid in cases with high intracranial pressure is well recognized but often ignored. Coning is better known at the foramen magnum with posterior fossa tumours, but it is probably more common and more dangerous at the hiatus tentorii in cases with supratentorial tumours, especially rapidly growing gliomas, also abscesses, middle meningeal haemorrhage, and acute subdural haematomas, all of which commonly produce very high pressure before papilloedema appears. The danger of coning can be avoided, first, by not doing lumbar puncture unnecessarily; secondly, by removing not more than the required minimum of 2 ml., drop by drop, using always a Greenfield needle of fine calibre with manometer to control the escape of fluid; and, thirdly, by not doing jugular compression (patency of the needle can be proved by abdominal compression). Jugular compression is commonly done in brain tumour cases, but it is valueless and potentially dangerous, and need never be used; in spinal cases, on the other hand, jugular compression is of vital importance and should never be omitted. In high-pressure cases we have seen several deaths directly attributable to lumbar puncture: death usually occurs after six to twenty-four hours and not immediately.

As is well known, the C.S.F. pressure may be high without papilloedema and, conversely, owing to spontaneous fluctuations, the pressure may be normal temporarily in patients with papilloedema; a single reading may therefore be misleading. Also, the lumbar pressure is sometimes lower than the intracranial pressure when the latter is high and is associated with partial coning at the hiatus tentorii (Smyth and Henderson, 1938).

The common practice after lumbar puncture of raising the foot of the bed to prevent headache should never be used in tumour cases, because that position raises the intracranial pressure still more; the head should be raised to lower the pressure.

Summary

Diagnostic lumbar puncture in cases of either suspected or known intracranial tumour is used more often than is necessary, and without due regard to its limited value and potential dangers. It is not part of routine neurological examination, and should always be used with discrimination.

Many tumours have normal fluid, while increased protein is often due to conditions other than tumour.

The value of spinal fluid examination in known tumour cases is negligible, except sometimes in confirmation of acoustic neurofibromas and in the identification of some deep cerebral glioblastomas invading the ventricle, and perhaps in the identification of pinealomas.

Although lumbar puncture is of very little value in specifically verifying or excluding intracranial tumour, or in the management of neurosurgical cases, it is nevertheless useful in preliminary investigation. The discovery of increased protein or high C.S.F. pressure may reveal an unsuspected organic lesion, possibly tumour, but normal fluid never excludes tumour.

Lumbar puncture has little value in the diagnosis of abscess, and it is often dangerous, as also in other cases of rapidly increasing intracranial pressure, owing to the onset of very high pressure before papilloedema appears. The danger attached to lumbar puncture should be carefully balanced against its limited diagnostic value.

Comments are made about the measuring of lumbar pressure and its value.

We wish to express our thanks to the staff of the National Hospital, and especially to Dr. J. G. Greenfield, for permission to use his records and for helpful advice.

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A draft Order in Council has been laid before Parliament giving the outline of the proposed arrangements for the next census in Britain, proposed to be held on April 8, 1951. Censuses are expected to be held on the same day in Northern Ireland, the Channel Islands, and the Isle of Man as well as in Great Britain. It is proposed to obtain information on the distribution of the people by area, sex, age, and marital condition; the size and composition of households; where people were born, where they live, and where they work; what their nationality is; their occupations and industries; whether they are still at school, college, etc., or, if they have finished whole-time education, at what age they finished; whether the dwelling is structurally separate, how many rooms it has, and whether the household has or shares a piped water supply, a kitchen sink, a cooking stove, a water closet, and a fixed bath. In the case of married women under 50 it is proposed to ask the date of marriage and the number of children. The questions that will be asked will relate to questions of fact and not of opinion and will be made as simple as possible. Though in total the questions will exceed those asked in 1931, they have practically all been asked at one or other of the previous censuses held in this century. Returns are required to be made for every person alive in the country at midnight ending the census day and for certain other persons who, though outside the country at that time, are normally resident in the country —for example, persons on a fishing or coastwise voyage. Particulars will be obtained of all Service men and women as well as of civilians.

EFFECT OF DIATHERMY CURRENTS ON METAL IMPLANTS IN THE BODY WALL

BY

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[WITH PHOTOGRAVURE PLATE]

With the development of biologically inert metals, increasing use is being made of these in surgery, ranging from pins, plates, and cups in orthopaedic work to skull plates. Especially is this so in the repair of herniae, mainly of the anterior abdominal wall. There is thus an ever-increasing chance that patients with such metal implants may be subjected to some form of diathermy treatment—for example, for fulguration of a bladder papilloma—or have short-wave diathermy prescribed for some chronic inflammatory complaint. Usually, advice is against such forms of therapy when it is known that the patient has metal embedded in his tissues. But what are the actual chances of burning around the metal?

To a physicist this is a clear-cut problem admitting of a definite answer. Diathermy currents of two main types are used in medicine—the long-wave and the short-wave forms.

Long-wave Diathermy.—This is used for cutting the tissues, coagulating the bleeding-points, and fulgurating tumours. In this type the tissues of the body form part of the electrical circuit, and the heating effect of the current varies with the resistance of the tissue or any foreign body lying in the path of the current. If the current, which is constant, is C, then the heating will vary as $C^2 \times R$, where R is the resistance of the particular tissue or material through which the current is flowing. The resistance of the skin and fat is much higher than that of any metal implant in the path of the current, and no deleterious rise in the temperature of the metal implant would be expected.

It is conceivable, however, should the end of a wire filigree protrude through the skin and come in contact with the pad forming the indifferent electrode, that sparking with consequent burning of the adjacent skin might occur round the protruding wire. Such an occurrence is extremely improbable. A more likely happening is inadvertently touching such a filigree with a coagulating button used for haemostasis in the course of a laparotomy. In such a case, if the bulk of the implant was small, some burning of the tissues in which the metal was embedded might occur.

Short-wave Diathermy.—This is used in two forms. The first is dielectric heating. In this the body is used as a dielectric between the plates of a condenser formed by two insulated electrodes, usually made of glass. The heating effect of the current depends on the dielectric constant of the tissue or material, good heating being obtained where the value of the constant is high and where the electrical resistance of the tissue or material is also high. Since a condenser with a metal dielectric cannot be charged and the electrical resistance for metals is low relative to the values of the body tissues, no harmful heating effect would be expected in and around a metal implant when this form of diathermy is used. The other way in which short-wave diathermy currents are used for heating is by electromagnetic induction, as in the machine known commercially as the inductotherm. This is an application of the principle employed in the electric induction furnace for smelting metals. The current is led around a coil in which the part to be heated is placed. The heating effect of the induced currents is most marked where there is a low resistance in the field. Here, therefore, the low electrical resistance of metal implants might be expected to produce a rise in temperature of the metal sufficient to cause damage to the tissues in its vicinity.

In all the above forms of diathermy as used in medicine the frequencies and wavelengths are not such as will produce any resonance effects. One point must, however, be emphasized. In the electromagnetic induction form the heating effect is enhanced if the metal can be magnetized—for example, stainless steel and similar alloys.

Experimental Tests

The effects of these three modes of application of diathermy currents have been tested on animals to ascertain how closely the results correspond with the above theories.

Eleven Wistar rats, each weighing 150 g., were used. The metals implanted were: (1) tantalum wire, diameter 0.003 in. (0.0076 cm.), length 10 in. (25 cm.); (2) stainless steel wire, diameter 0.01 in. (0.025 cm.), length 6 in. (15 cm.); and (3) tantalum wire gauze, 50 by 50 mesh, made from 0.003-in. diameter wire; a piece ½ by ½ in. (1.25 by 1.25 cm.) was used. In each case the right side of the lower part of the back was the site of the implant (Fig. A). The stainless steel wire was made into a coil ¼ by ¼ in. (1.9 by 1.9 cm.) and inserted just under the deep fascia of the muscles of the back. The tantalum wire was darned into the deep fascia to form a patch ½ by ½ in. The tantalum gauze was inserted just deep to the deep fascia (Plate, Fig. 1).

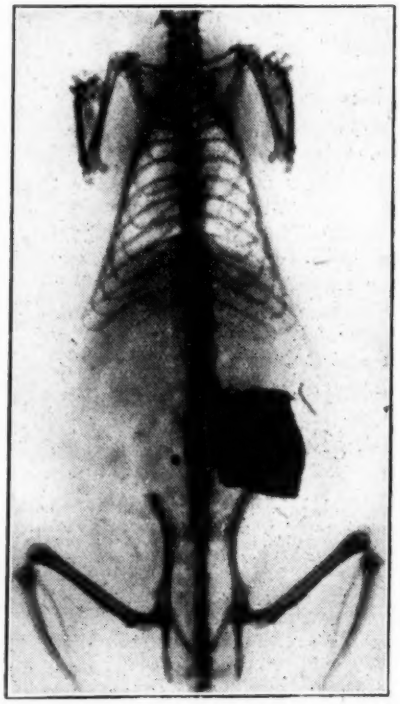

FIG. A.—Site of implant (tantalum gauze).

After three weeks the control animals were killed—one from each of the three groups of implants—and the tissues in the region of the metal examined histologically (Plate, Fig. 2).

The rest of the animals were subjected to the various forms of diathermy, killed in 72 hours after this, and the tissues adjacent to the metal examined for any evidence of burning, naked-eye and microscopically.

Application of Long-wave Coagulation Diathermy.—One rat was selected from each of the three groups of implants. The large electrode, of silver, 1 in. (2.5 cm.) in diameter, was covered with a saline-soaked pad and applied to the skin directly over the metal implant. With the animal under chloroform anaesthesia (this was used in all cases) the diathermy button was advanced up the tail, producing coagulation. The current was passed for three minutes, during which time 2 in. (5 cm.) of tail had been

treated. *Result* :—The histological appearances were the same as those shown by the controls (Plate, Fig. 2). No burning had occurred.

Application of Short-wave Dielectric Heating.—Glass electrodes of 2-in. (5-cm.) diameter, 4 in. (10 cm.) apart, were arranged so that the current passed through the animal's body and the metal. In these experiments only tantalum gauze was used. Three animals were treated. In the first and second, current of a strength usually employed on human beings was passed for five and ten minutes respectively. No rise in general body temperature occurred. In the third rat the current, greatly in excess of that ever used on man, was passed for five minutes, at the end of which time the animal's rectal temperature was 105° F. (40.6° C.). *Result* :—No evidence of burning was found in any of the animals in the region of the implant or elsewhere.

Application of Electromagnetic Induction Heating.—Two animals were used, both of them with tantalum gauze implant. The maximum output that could be obtained from the machine (Victor inductotherm) was passed through a coil made up of three turns of wire, in the centre of which the animal was placed. In the one, the current was passed for five minutes; in the other, for ten minutes. *Result* :—No burning occurred in either animal.

Summary and Conclusions

It would thus appear to be safe to use any of the above forms of medical diathermy on patients with metal in their body walls, in the small amounts and in the form of wire of fine diameter, such as is likely to be employed in the repair of herniae. The absence of any burning in the electromagnetic induction experiments is probably due to the rapid conduction of heat away from the metal by the body fluids. It must be admitted, however, that the above experiments do not exclude the possibility of harmful effects in cases in which the metal insert is large and is implanted in relatively avascular tissue such as bone. Considerable heating might then occur and cause necrosis, especially if the metal can be magnetized, as, for instance, in the commonly employed stainless steel tri-fin nail used in the treatment of fracture of the neck of the femur.

I wish to express my thanks to Professor Cappell and Mr. W. W. Galbraith, heads of the departments of pathology and urology, for their interest and criticism of this article; to Dr. J. M. A. Lenihan, physicist to the Western Infirmary, Glasgow, for his help in the physics involved; and to Miss Ritchie, of the *x*-ray department, for the skiagram reproduced above.

Fifteen overseas students are taking part in a survey of British voluntary social services arranged by the British Council between June 16 and June 30. The students, who come from 11 countries, are taking long courses of study in this country in subjects which include law, local government, science, youth organization, and social science. The first visit was on June 19 to the Wimbledon Guild of Social Welfare, and St. Pancras Rotary Club entertained the group to lunch the following day. Other visits were to the British Red Cross Society on June 21, Dr. Barnardo's Garden-City Home at Ilford on June 23, and the clinic of the People's Dispensary at Ilford on June 24. On June 26 the students will visit the headquarters of the W.V.S., and in the evening they will visit boys' and mixed clubs in London. On June 28 they will be shown over the British Legion Village, near Maidstone, Kent, and the survey concludes with a visit to the National Institute for the Blind. The countries from which the students come are: Ceylon, China, Egypt, Finland, India, Indonesia, Mauritius, Norway, Persia, Siam, and the U.S.A.

HISTOLOGICAL REACTIONS TO INJECTIONS OF PROCAINE PENICILLIN IN OIL

BY

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[WITH PHOTOGRAVURE PLATE]

Procaine penicillin, suspended in a vegetable oil and given by intramuscular injection, is now widely used. Review of the literature yields little information regarding the histological reaction of human tissues to injections of therapeutic substances suspended in oil and apparently none about the effects on human or animal muscles of procaine penicillin in oil. There are, however, reports of the changes produced by vegetable oils in animals and by penicillin in both man and animals.

This paper gives an account of the histological changes occurring in the deltoid muscles and adjacent lymph nodes of a patient who had received intramuscular injections of procaine penicillin in arachis oil. The commercial preparation used contained 300,000 units of penicillin G in combination with 120 mg. of procaine suspended in 1 ml. of arachis oil.

Clinical Summary

A foreman builder aged 67 was admitted on May 3, 1949, with subarachnoid haemorrhage complicated by a respiratory infection leading to empyema. While in hospital he was found to have an aneurysm of the aorta. His general condition deteriorated, bed-sores and a urinary infection developed, and he died on June 26, 1949.

He received the following treatment. On May 7 and 8 50,000 units of penicillin in saline were given every three hours intramuscularly on 16 occasions and then discontinued. A total of 85 g. of sulphadimidine was administered orally over the next eight days to May 15. From May 16 to 24 10,000 units of penicillin in saline were given intramuscularly three-hourly; the dose was then increased to 30,000 units three-hourly until June 2. These intramuscular injections were made into the buttocks, thighs, and deltoid regions. On June 2 procaine penicillin in arachis oil was substituted, 300,000 units being administered intramuscularly once daily and continued until June 16, when the dose was doubled to 600,000 units daily. This was maintained until the patient's death on June 26. During the last 14 days, because of extensive bed-sores over the sacrum and buttocks, many of the injections of procaine penicillin in oil were made into the deltoid muscles. No reaction was noted clinically at the sites of injection.

Pathological Findings

A necropsy which was performed on June 28 showed a wasted man with large bed-sores over the sacrum and buttocks. There were several needle-marks in a small area over both arms above the deltoid insertions. The clinical findings of subarachnoid haemorrhage, aortic aneurysm, and empyema were confirmed. Underneath the needle-marks seen on the skin of each deltoid region was an area in the muscle about 6 by 3 cm. which was greasy to the touch and showed some free oil in its deeper part. No scarring of the muscle was obvious macroscopically, but some minute cystic areas and one small haemorrhage were observed. The remainder of the muscle appeared normal. The right and left axillary lymph nodes were not enlarged: several were taken from each lateral group for microscopical examination.

Histological Appearances

From the affected areas of both deltoid muscles several blocks of tissue were examined and all showed similar appearances. The muscle was oedematous and the perimysium

contained a large number of oily globules (Plate, Fig. 1). In the paraffin sections these were represented as spaces and in frozen sections as round areas staining bright red with Scharlach R. They varied in size from over 2 mm. down to extremely finely divided droplets. This oily material was associated with a marked cellular reaction in the connective tissue and some degeneration of adjoining muscle bundles (Fig. 2).

The cellular reaction varied little from one area to another, being composed mainly of small round cells and large mononuclear phagocytes with smaller numbers of eosinophils and a few multinucleate giant cells. In some places, however, eosinophils were particularly numerous, and in those areas immediately surrounding the oil globules large mononuclear and multinucleate phagocytes were predominant (Fig. 3). There was no evidence of any acute inflammatory reaction, neutrophil leucocytes being scanty. Around some globules there was little cellular reaction, but around others it was pronounced. The muscle bundles associated with the areas of cellular reaction showed disintegration and disappearance of muscle fibres and some replacement by cellular fibrous tissue. The oily material was being taken up by many of the cells, which in the frozen sections were seen to be distended by finely divided oil. There was little evidence of chemical breakdown of the oil. Fatty acid crystalline deposits were not found, but a few small areas staining deeply with haematoxylin suggested the presence of calcium salts. In frozen sections of the muscle stained by Nile-blue sulphate some of the oil was coloured blue. These lesions were localized: the muscle a short distance beyond the edge of the oil was histologically normal.

The axillary lymph nodes had some "sinus catarrh" with large numbers of foam cells mainly in the peripheral sinusoids. Frozen sections confirmed that these cells contained very finely divided globules of oil.

Discussion

The histological changes observed in this case may have been due to either or both of the constituents of the injection—namely, procaine penicillin and arachis oil. Concerning arachis or similar vegetable oils, there seem to be reports in the literature of animal experiments only. Brown *et al.* (1944) have studied the reaction of rabbits and rats to several vegetable oils injected intramuscularly. In all, the results were similar but differed in intensity. After 24 hours there was a moderate increase in round cells and the oil was diffusely scattered through the muscles, tending to accumulate along fascial sheaths and also between muscle bundles. By the third day the oil was in small cyst-like droplets surrounded by a layer of fibrin and large cells of epithelioid appearance; outside this were leucocytes and wandering cells. The leucocytic reaction reached a peak between the third and sixth days and then subsided slowly. In rats, but not in rabbits, arachis oil induced some muscle necrosis and oedema.

Romansky and Rittman (1944) have described similar tissue changes in hamsters following intramuscular penicillin in a beeswax–peanut-oil mixture, but muscle necrosis was not a feature Working with albino rats, Emery *et al.* (1942) found that oil cysts up to 2 mm. in diameter, and persisting for several months, were produced in response to four different vegetable oils injected intramuscularly. Deanesly and Parkes (1933) have described oil cysts in rats and mice following the subcutaneous injection of olive, sesame, and castor oils. The last remained in the tissues for long periods.

According to Anderson (1949) minute cysts with thin fibrous walls have been found in the muscles of patients dying one to two months after the injection of penicillin in beeswax and peanut oil. These may have been oil cysts of the kind found in animal experiments.

In the human subject muscle necrosis at the site of injection of penicillin has been recorded. Nelson-Jones and Williams (1945) have described aseptic muscle necrosis at the site of administration of penicillin by continuous intramuscular drip. Call and Gilbert (1947) reported two cases which received intramuscular penicillin and developed multiple abscesses three to four weeks later at the sites of injection. Cutting *et al.* (1945) gave rats daily subcutaneous injections of penicillin for six months and found haemorrhages, foreign-body giant cells, and excess of fibrous tissue in the injected areas. They have suggested that these changes may be due to trauma or mild infection, as no sterile precautions were taken.

I have not been able to find an account of the histological effects, if any, produced by intramuscular procaine in man or animals.

The histological changes recorded in the present case resemble those produced in rats by arachis oil, but differ in two features. First, the muscle degeneration and oedema are more extensive. Secondly, in animal experiments eosinophils were inconspicuous, whereas in the case reported they were numerous. The muscle degeneration and oedema are not surprising, as owing to the bed-sores on the thighs and buttocks this patient had more than one injection of procaine penicillin in oil into the area of muscle examined. (Most manufacturers advise against this, but, as in this case, it may occasionally be unavoidable.) It is not possible here to decide whether the procaine penicillin itself was wholly, partly, or not at all responsible for the cellular reaction and muscle changes. In view of the animal experiments with oil alone it is unlikely that procaine penicillin was wholly responsible.

The eosinophil reaction may have arisen in response to the arachis oil, though this has not been reported in experiments on rats or rabbits. On the other hand, penicillin is a known cause of eosinophilia and is perhaps a more likely cause for the eosinophils in this case. Orland *et al.* (1944) have described allergy to procaine, but there is no record of procaine causing an eosinophilia. Frozen sections showed that the oil was being actively taken up by the phagocytic cells and had been carried to the adjacent lymph nodes. It is possible that phagocytes may ultimately remove all the oil and damaged muscle and a fibrous scar remain.

Summary

The histological changes following the intramuscular injection of procaine penicillin in arachis oil are described.

The oil occurred in small cysts surrounded by a cellular reaction in which eosinophils were conspicuous. Some muscle degeneration and oedema were present. Fat-bearing phagocytes were plentiful around the oil and in adjacent lymph nodes.

The histological features have been compared with the reactions of animal tissues to arachis oil and penicillin which have been described separately by previous observers.

I am indebted to Dr. G. S. Sansom for the photomicrographs and to Dr. R. J. R. Cureton for helpful advice and criticism.

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SECONDARY BRONCHIAL CARCINOMA SIMULATING A STRANGULATED FEMORAL HERNIA

BY

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AND

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[WITH PHOTOGRAVURE PLATE]

Introduction (A. G. S.)

It is well recognized that bronchial carcinoma is a most protean tumour, perhaps the most protean of all in respect of its metastases, which are not infrequently the first manifestation of the disease. A very large literature has grown up on this subject and we hesitate to add to it, but this case was so unusual and so misleading in the manner of its presentation of this fell disease—so apt first to show itself as a metastasis before the primary tumour is known—that we thought it worth recording for the guidance of others who may perhaps meet its fellow. Another point is that the biopsy pointed quite clearly, dramatically, and unexpectedly to the site of the primary tumour.

Our final justification lies in the statement of Professor Willis (1948), who says: "Because of the frequent misdiagnosis of this disease [and later he refers to glandular metastasis more specifically in this respect], only fully proved necropsy records are of any value for the analysis of its properties." These will be duly presented.

Clinical History

A married woman aged 76 had noticed some three weeks previously a tense and increasingly painful lump in the left femoral region, which enlarged rapidly. On August 8, 1949, she was seen by me (E. W. H.) in consultation with her own doctor, Dr. Ethel Downing, of Eastbourne.

She was admitted to the Princess Alice Hospital the same day as a case of femoral hernia, the notes recording that a large reddish lump was found in the left femoral region, very tense and irreducible, and probably of omental origin, as there was no history of vomiting.

Operation was performed the same day, and on incising over the tumour fluid squirted out under great pressure; it was thick, yellow, and haemorrhagic, but odourless. It was found to be a degenerating glandular mass, which was completely excised down to normal tissue. The wound was drained, and then closed with interrupted sutures, sulpha–penicillin powder having been installed. During after-treatment 2,700,000 units of penicillin were given. The specimen was sent to the pathologist for examination.

Pathological Report (A. G. S.).—The specimen consisted of a large portion of fat and a smaller portion of new growth, measuring 2½ by 1½ in. (6.25 by 3.75 cm.). On section the latter was soft in consistence and white in colour. *Histology.*—The tumour seemed to be a lymph gland, heavily invaded by a bronchial carcinoma showing two phases: (1) polymorphic and oat-cell anaplasia, and (2) squamous metaplasia (Plate, Figs. 1 and 2). It was held to be a bronchial carcinoma of Grade 4 malignancy (Broders's classification).

The chest was accordingly *x*-rayed on August 19 by E. O. F., who reported as follows: "There was uniformly increased density in the right lower lobe consistent with a localized area of atelectasis and probable bronchial carcinoma. Adhesions were present at the left costo-phrenic angle" (Plate, Fig. 3).

Subsequent History

The wound broke down and the edges sloughed. The patient became somewhat "mental" and persisted in playing with the dressing. She recovered well from the operation and her condition gave no cause for alarm until just before death. There were no chest symptoms at any time until then. The patient went slowly downhill, looking unwell, but with no definite symptoms or signs—for example, anorexia or wasting. Atelectasis of the lower lobe was not found clinically.

On the afternoon of the day of death the patient became drowsy and comatose, but with good pulse and no other signs. She died suddenly at 10 p.m. on September 8, exactly one month after admission to hospital. Her pulse and temperature were raised the day before death.

Post-mortem Examination

The body was that of an elderly woman (5 ft. 9 in.—175 cm.) showing good nutrition; rigor mortis and posterior hypostasis were present. Cutaneous cachectic pallor was marked. In the left femoral region, sloping down and outwards, there was an elliptical wound 4 by 2 in. (10 by 5 cm.), which is gaping and at the bottom of which is an ulcerating neoplastic area.

Owing to removal of the heart and lungs *in toto* the former was not examined, but appeared to be unaffected by neoplasm so far as the pericardium was concerned and not obviously enlarged.

Lung.—One and a half inches below the bifurcation of the right main bronchus the mucosa was mottled with new growth. Just below this there was a scirrhous stricture of new growth,

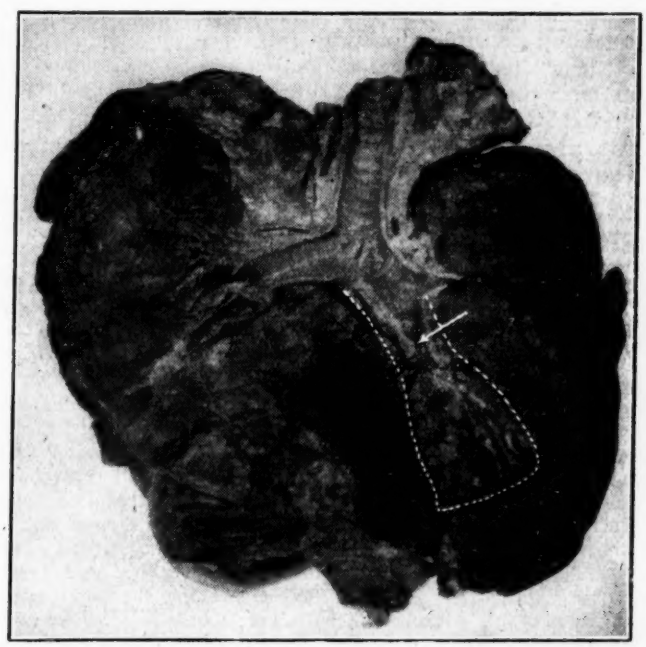

FIG. A.—Right lower lobe of left lung: atelectasis and neoplasm.

below which was a large wedge of white, soft necrotic growth which was breaking down. This was in the right lower lobe, confirming the *x*-ray report of atelectasis (Fig. A). Microscopy showed an oat-cell carcinoma (Plate, Fig. 4).

Liver.—In the free border of the left lobe there was a whitish tumour about the size of a halfpenny. This was expected to be a secondary deposit, but was in fact an adenoma of the liver.

Brain.—Except for marked atheroma of the circle of Willis, and elsewhere some general atheroma of the aorta, no pathological changes apart from senility were found, nor were there any other metastases—for example, cerebral.

Discussion

Although the very limited size of the primary growth would seem to favour operative procedures such as lobectomy, the patient's age and rapid decline clearly ruled this out.

The precise cause of death is not clear, but the soft necrotic growth in the lung was probably producing considerable toxaemia, which affected the myocardium of an elderly subject. The route of metastasis was probably haematogenous.

We are greatly indebted to Dr. J. E. McCartney, of the Southern Group Laboratory, Park Hospital, for the photomicrographs of the primary and secondary tumours and to the local hospital photographic service of Messrs. Turnham, of Eastbourne, for the photograph of the specimen. We are also indebted to Messrs. Ilford Ltd. for the *x*-ray photograph.

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SJÖGREN'S DISEASE ASSOCIATED WITH A NUTRITIONAL DEFICIENCY SYNDROME

BY

R. B. RAFFLE, M.B., M.R.C.P.

In 1933 Henrik Sjögren first described the disease which bears his name. The eye changes were first noted, but the condition was later found to involve a large number of other structures. The non-ocular features have been stressed in later papers by Sjögren and by Weber (1945). The present case, which was seen in general practice and which is unassociated with eye changes, shows certain clinical features which seem worthy of record.

Case Report

The patient, a spinster of 50 working as a charwoman, first reported in January, 1949, complaining of depression and vague "rheumatic" pains affecting the occipital, interscapular, and sacral regions. She felt weak, lacked appetite and energy, and was subject to early morning wakening. These symptoms had been present for about three months.

Pronounced facial swelling affected both parotid regions, and on inquiry she stated that this had started first on the left side of the face in July, 1947. The initial attack had been diagnosed as mumps, but the swelling had never subsided completely. Instead there had been recurrent exacerbations with incomplete regression, and some weeks later the right side of the face became similarly affected. Later the patient noted swellings under her chin. There had never been any pain. Some weeks after the onset of the swelling she had noticed dryness of her mouth, which became worse and caused difficulty in swallowing and speaking. The dysphagia had become intensified in the last few weeks, and was then associated with a feeling of food sticking behind the larynx. During this time she had persistent soreness of the tongue.

There were no gastro-intestinal symptoms and no paraesthesiae, but for many years she had been subject to a typical Raynaud phenomenon in the fingers during cold weather. She had also had what seems to have been a distal pulp abscess affecting the left middle finger in November, 1948, since when the finger had been persistently cyanotic and subject to attacks of burning pain on warming. It was involved in the "local syncope" of the Raynaud attacks in common with the other fingers, but the attacks lasted longer in this finger and never recovered beyond the stage of cyanosis. The menopause had occurred two years previously. She had never been subject to eye trouble.

Examination on January 19 revealed a spare, pale, nervous woman, looking older than her years and possessing a conspicuous swelling in both parotid regions. Each parotid gland was enlarged to the size of half an orange, and was firm and nodular but not tender. Both submaxillary glands showed a similar plum-sized enlargement. The whole buccal cavity was dry, and the mucosa was dull red in colour and of a matt texture. The tongue was dry, red, and glazed, the papillae not being evident. She also showed an angular stomatitis and cheilosis. The skin was dry, the hair thin, and the eyebrows normal. The left middle finger was cyanosed and the finger-nails showed koilonychia. The heart, lungs, and abdomen revealed no abnormality. The blood pressure was 135/85. The spleen was not palpable.

Blood examination showed: haemoglobin, 70% (Haldane); red cells, 4,200,000; colour index, 0.83; white cells, 5,000 (polymorphs 72%, eosinophils 1%, lymphocytes 15%, monocytes 12%). E.S.R. (Westergren; 200 mm. column): 1 hour reading, 20 mm. The Wassermann reaction was negative. A chest *x*-ray film revealed no abnormalities. Urine examination showed nothing abnormal.

Progress.—The patient was at first given vitamin A, 150,000 units daily. On February 7 she was not improved in any way, and vitamin A therapy was stopped and ferrous sulphate, 18 gr. (1.2 g.) daily, was administered. On February 23 the haemoglobin was 85% and the red blood cells numbered 4,500,000. There was no improvement in the buccal condition, but she felt subjectively better. "Beplex" capsules, six a day, were given. This provides a daily intake of 6 mg. of thiamin hydrochloride, 4.8 mg. of riboflavin, and 60 mg. of nicotinic acid.

On March 5 the haemoglobin was 105% and the red blood cells numbered 4,800,000. She felt much more "like herself," looked better, was sleeping well, and was no longer fatigued. The soreness of the tongue had gone and also the angular stomatitis and cheilosis, but the xerostomia persisted and the glandular enlargement was unaffected. Her appetite was improved and the dysphagia less troublesome; she attempted to take a more normal diet, and reported that the sensation of food sticking behind the larynx had vanished. Three beplex capsules and 9 gr. (0.6 g.) of ferrous sulphate were continued daily, and the improvement was maintained.

Discussion

The course of the illness seems to fall roughly into two stages—the first, which had started in July, 1947, comprising the gradual increase in size of the salivary glands together with the xerostomia; the second, beginning in October, 1948, and associated with the complaints of fatigue and general ill-health. During this second period the soreness of the tongue and the finger infection had developed.

The salivary gland changes are compatible with the diagnosis of Sjögren's disease, the ocular features of which are sometimes delayed, xerostomia being the presenting symptom. The age, sex, and psychological type of the patient also point to this diagnosis, and the association with Raynaud's phenomenon has been noted before. As Ellman and Weber (1949) point out, it is doubtful how far the condition can be distinguished from Mickulicz's disease.

The glossitis, angular stomatitis, cheilosis, koilonychia, and hypochromic microcytic anaemia of the second stage are clearly the result of nutritional deficiency. In view of the part allegedly played by vitamin deficiency (e.g., hypovitaminosis A) in the aetiology of Sjögren's disease, inquiry was made into the dietary history. In spite of the fact that the patient was a spinster, living alone and doing part-time domestic work, this was good, and there was no evidence to support the existence of any gross primary nutritional error preceding the onset of the glandular swelling, or, indeed, prior to 1948. During that year, however, the

xerostomia had made chewing and swallowing difficult and she had had to keep largely to liquids. It was therefore considered that the xerostomia had resulted in the nutritional deficiency syndrome of the second stage. The addition of iron and vitamin B complex greatly improved these deficiency features. Iron and riboflavin appear to be the main deficient factors. The picture was very similar to that of the Plummer–Vinson syndrome, though it occurred at a later age period than is usual with the latter condition, which tends to improve spontaneously after the menopause.

It has been suggested (Stannus, 1940; Pollak, 1945) that iron deficiency may condition disturbance in the metabolism of riboflavin and allied factors; the haemin derivatives cytochrome and cytochrome oxidase are linked in tissue respiration with enzyme systems containing riboflavin and nicotinic acid, and riboflavin may be a weak link in the chain. The cause of the nutritional disturbance in this case seems to be the dysphagia secondary to the xerostomia, whereas in the usual younger case of Plummer–Vinson syndrome other factors (e.g., demands of pregnancy, lactation, and menstruation) are responsible. It is interesting to note that in what has been referred to as the second stage of this illness the dysphagia became intensified and was associated with the sensation of food sticking behind the larynx—a feature which is characteristic of the Plummer–Vinson syndrome. The dysphagia in the latter condition seems to result from B-complex (particularly riboflavin) deficiency and does not appear to be the primary factor in the pathogenesis of the condition.

As has also been noted by other observers (e.g., Ellman and Weber, 1949), the glandular enlargement was unaffected by vitamin A therapy. It would seem that the cause is not to be looked for in nutritional deficiency, but, in view of the often striking psychological disturbances which these patients show, investigation from the psychosomatic angle and attention to the aspect of autonomic imbalance may be profitable.

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Medical Memoranda

Herpes Gestationis with Hydatidiform Mole and Chorion Epithelioma

Herpes gestationis has been described by Duhring as a condition which differs from dermatitis herpetiformis only in so far as pregnancy is the exciting cause. It is a fairly uncommon condition, and associated with hydatidiform mole and chorion epithelioma is an extreme rarity. Elliott (1938) describes an extensive bullous eruption associated with chorion epithelioma and metastases. A further case is reported by Whitfield, Smith, and Manson (1946).

CASE REPORT

The patient, a woman aged 42, had had two previous pregnancies, in 1934 and 1936, and one miscarriage in 1946. In August, 1948, she consulted Mr. Keith Vartan on account of menorrhagia, and was admitted to hospital on October 21. The Friedman test was then found to be positive. Loss of blood continued, and she was treated by transfusion. On November 5 a hydatidiform mole was removed from the uterus. Penicillin was given, and on November 12 she was found to have developed a generalized herpetiform eruption, mostly on the limbs and around the waist. The lesions consisted of circular red patches most of which, after a day or two, developed into vesicles.

On November 26 dilatation and curettage were performed, but only one or two small vesicles were obtained in the curettings. On December 2 a Friedman test was negative. I saw the patient on December 17, when the clinical picture was typical of herpes gestationis. She was transferred to St. Nicholas' Hospital on December 22. In view of the stress laid on the danger of chorion epithelioma developing in these cases, it was thought essential that another Friedman test should be performed, but unfortunately the patient discharged herself at Christmas and was not heard of again until some weeks later, when she had been admitted to another hospital on account of recurrence of uterine bleeding. She was there found to have a soft, large uterus, which was curetted, several small vesicles, typical of hydatidiform mole, being obtained.

Histologically, a differentiation between hydatidiform mole and chorion epithelioma could not be made. The Friedman test was positive, and it was therefore decided to remove her uterus, which was found to be moderately enlarged with a thick firm wall. The uterus was filled with a nodular semicystic growth which had a mottled haemorrhagic appearance. Macroscopically, it suggested a mole which was invading the uterine wall. The histologist decided that the condition should be regarded as a chorion epithelioma. A Friedman test taken a fortnight after operation was still positive. There was still evidence of a rash when the patient was admitted to the third hospital, and this persisted without change during her stay there. Shortly before her discharge from a fourth hospital, to which she had been transferred for *x*-ray treatment, it was observed that the rash had cleared up, but that there was residual pigmentation of the skin.

I wish to thank Mr. Keith Vartan, Dr. E. J. Newton, Mr. M. N. Rankin, and Dr. T. S. Leedham for the information they have given me about this patient.

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Primary Septicaemia and Meningitis Due to Salm. Enteritidis

A basal meningitis due to *Salmonella enteritidis* has been reported on a number of occasions. Smith (1921), Lynch and Shelburne (1930), Stevenson and Wills (1933), and Schulz-Schmidtborn (1934) each report one case. Huang *et al.* (1937) report two cases associated with relapsing fever. The ages of these cases vary from 5 weeks to 30 years.

Salm. enteritidis septicaemia, as noted by other observers, usually occurs in association with a debilitating disease. The following case illustrates this point, a severe degree of anaemia being present for the greater part of a year previously and the patient suffering from a low-grade pyrexia for three months prior to death. The septicaemia was primary and there were no intestinal symptoms until 48 hours before death. Until a positive blood culture was obtained an interesting sequence of events occurred to obscure the diagnosis.

CASE REPORT

The patient, a girl aged 17, underwent splenectomy for an idiopathic haemolytic anaemia in December, 1948. After the operation she developed, first, a thrombosis in the deep veins

of the right calf, and then a mild urinary infection. She was discharged on January 28, 1949, still with a slight evening pyrexia but with a haemoglobin of 90%.

On March 19 she was readmitted to hospital with a pyrexia of 99–100° F. (37.2–37.8° C.) and generalized aches and pains in the muscles and joints. Repeated blood cultures, serum agglutinations, blood counts, throat swabs, and urinary examinations were all negative, apart from an increasing degree of anaemia. Stool examinations were not carried out. A provisional diagnosis of Still's disease was made. The *x*-ray report stated: "Knees and wrists show calcium shift without, however, any significant joint change consistent with a generalized infective arthritis." On May 3 a biopsy of the neck gland under general anaesthesia was carried out. On the morning of the 5th the temperature rose to 102° F. (38.9° C.) and the right eyelid was noted to be swollen. Bacteriological examinations of the throat and urine revealed nothing of pathological significance. The leucocyte count was normal. Blood cultures were taken. Next day the temperature was 104° F. (40° C.), both eyelids were very swollen, and the conjunctivae were oedematous. The father now stated that the patient's mother was allergic to anaesthetics, the allergy taking the form of oedema of the eyelids. It was then recalled that after her splenectomy the patient had suffered from a marked conjunctivitis. With this in mind "antistin" was given.

On May 9 *Salm. enteritidis* was identified in the blood cultures. That evening diarrhoea began and the same organism was isolated from the faeces. Death occurred 48 hours later.

A post-mortem examination, carried out 12 hours after death, showed well-marked autolysis and discoloration of the small intestine and anterior abdominal wall. Death was due to a purulent basal meningitis, the causative organism being the *Salm. enteritidis*. No other foci were found in the body.

The organisms isolated from the blood, faeces, and meninges were all shown to have the antigenic structure—O IX, XII; H g, m—with biochemical reactions of the Danysz variety.

The source of infection was never satisfactorily established, mainly it was felt owing to the time between invasion and diagnosis.

I wish to thank Dr. R. G. M. Longridge, physician to Salisbury General Hospital, for permission to publish this case; Dr. L. H. D. Thornton, director of the Salisbury Area Pathological Service, for advice and criticism; and Dr. Joan Taylor, of the Salmonella Reference Laboratory.

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Rheumatoid Arthritis Treated with Anterior Pituitary Growth Hormone

After reading the leading article (1949) on recent discoveries of the effects of cortical hormones on rheumatoid arthritis I am prompted to describe a case unsuccessfully treated with anterior pituitary growth hormone.

Barsi (1947) described a series of cases of rheumatoid arthritis which improved considerably after the transfusion of blood from pregnant women. It seems reasonable to suppose that such improvement was most likely due to some hormone circulating in increased quantity during pregnancy. Most of the sex hormones and many others, such as thyroid, have already been tried in rheumatoid arthritis, without much success. It was therefore decided to turn to the pituitary, which is known to have much increased activity during pregnancy.

The many hormones produced by this gland were reviewed in order to find which might most likely influence a disease of the skeletal system. The growth hormone of the anterior lobe influences the growth and development of bones; and in rheumatoid arthritis, indeed, there is rarefaction of the bone underneath the affected joint surfaces. It therefore seemed worthy of trial. The preparation used was "antuitrin growth," which is both expensive and difficult to obtain. As a result only small doses were used, even less than the recommended ones.

CASE REPORT

A married woman aged 43 had had typical rheumatoid arthritis affecting principally the fingers of both hands, wrists, knees, and right shoulder for three years. It started at the age of 40, three months after the birth of her only child. The only treatment she had undergone was some indifferent physiotherapy. She was considerably disabled by the disease, being unable to put on her coat unaided or to turn a key in a lock, but there were no permanent deformities. The E.S.R. was 13 mm. in 1 hour (Westergren); Hb, 66%; blood cholesterol, 198 mg. per 100 ml. The association with the puerperium suggested a possible endocrine basis for the disease. There were no menopausal symptoms.

The diagnosis was confirmed by an eminent physician, who advised against chrysotherapy, in view of the low E.S.R., and suggested physiotherapy. This was given for the next three months, during which time thyroid extract and hexoestrol were given in fairly large doses. There was little improvement. The E.S.R. was then 9 mm. in 1 hour; Hb, 82% (after iron therapy).

Thyroid and hexoestrol were discontinued and 1 ml. of antuitrin G was given by subcutaneous injection. She stated that there was some heaviness and soreness in her knees and wrists about 12 hours afterwards, but there were no other effects. Thereafter she received 2 ml. of antuitrin G weekly for seven weeks. At the end of this time there was no change in her condition, and the E.S.R. was 20 mm. in 1 hour. She experienced no further effects in the joints from subsequent injections. These were now increased to 2 ml. twice weekly, and this was continued for four weeks, with no improvement. The E.S.R. was now 20 mm. in 1 hour. (This had often been estimated in between but little variation was found.)

No further antuitrin G was given, and one month later chrysotherapy was instituted. From this she has benefited greatly, her E.S.R. remaining steady at about 10 mm. in 1 hour, and at the end of the first course of 1 g. of calcium aurothiomalate she was able to put on her coat unaided and to turn a key in a lock. She had not been able to perform either of these acts during the whole time that she was under observation.

During the period of this record the patient underwent continuous physiotherapy, which undoubtedly played a large part in alleviating stiffness of the joints and, doubtless, in preventing subsequent deformities.

COMMENT

The administration of anterior pituitary growth hormone in small doses over a period of three months produced no improvement. In view of the fact that very large doses of "cortisone" are required to effect improvement in this disease, and the complete failure of smaller ones, it would be interesting to observe whether much larger doses of anterior pituitary growth hormone might have any effect. However, this was not possible under the conditions of this trial.

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Reviews

ADRENAL INSUFFICIENCY

The Diagnosis and Treatment of Adrenal Insufficiency. By George W. Thorn, M.D., with the collaboration of Peter H. Forsham, M.D., M.A.(Cantab.), and Kendall Emerson, jun., M.D. (Pp. 171; illustrated. £2.) Oxford: Blackwell Scientific Publications. 1949.

This is a valuable book on Addison's disease by a competent physician who has carried out original work with conspicuous success. The lucid and relevant presentation has been achieved in a small volume, well printed and illustrated. In selecting the references the author has omitted some which might well have been included to give a better balance to the indications of the development of clinical and therapeutic knowledge in this subject. On the historical side, Addison's monograph of 1855 is mentioned, but it is unfortunate that his earlier paper of 1849 to the South London Medical Society is ignored. It is of interest to be reminded that in 1896 William Osler prepared a glycerin extract of fresh hog adrenals and wrote a paper "on six cases of Addison's disease, with the report of a case greatly benefited by the use of suprarenal extract" in the *International Medical Magazine* of 1896 (5, 3).

Thorn rightly warns surgeons that removal of a functioning adrenal tumour may lead to temporary adrenal insufficiency until the adrenal gland on the opposite side has had time to recover its full function. He writes that secondary deficiencies of gonadal function are rare, but this is less true of Addison's disease developing at puberty or adolescence. The low urinary 17-ketosteroids is recorded as a frequent finding, particularly in females. Owing to hypersensitivity to insulin, Thorn writes, "In our opinion the standardized intravenous tolerance tests should never be employed in Addison's disease except for experimental purposes, because of the grave danger of inducing severe hypoglycaemia." This is certainly prudent, but the danger is greater in primary hypopituitarism, where it is customary to use half the standard dose in such diagnostic tests. A modified Cutler–Power–Wilder test is apparently advocated, but this is not without danger, and the Kepler test is now usually preferred. It gives similar information within 24 hours instead of 3 days. The epinephrine test is relatively new; an injection of 0.2 mg. lowers the eosinophil count in a normal individual by producing a secretion of adrenocorticotrophic hormone, but not in a patient whose adrenal glands are destroyed by tuberculosis or atrophy.

The treatment section is comprehensive, but it is unfortunate that Thorn has not modified his original recommendation that for every 0.5 mg. of desoxycortisone injected daily a pellet of 125 mg. should be implanted. This correlation will lead to overdosage with retention of fluid and hypopotassiaemia in a number of cases, even when time is given for stabilization before the implantation. For 1 mg. injected, one 100-mg. pellet is a more prudent calculation and even this may prove too high. The incision in Thorn's clinic for implanting tablets is said to be 2–4 cm. in length, but 1 cm. is big enough for the abdominal or thigh sites, and is advisable when repeated implants at intervals of six to eight months are contemplated. In America a lipo-adrenal extract (Upjohn) prepared from hog's adrenal glands is on sale, though expensive. It must be given intramuscularly. Its advantages are its small bulk and greater influence on carbohydrate metabolism than the usual aqueous extracts. Thorn finds that 1 ml. is equivalent to 5 to 10 ml. of the latter. It is slow-acting, reaches its peak in 4 to 6 hours, and lasts 8 to 12 hours. It is therefore of value in patients who tend to spontaneous hypoglycaemia, and cortisone may be of even greater value if its synthesis on commercial lines is achieved.

S. LEONARD SIMPSON.

CHEMICALS AND CELLS

Chemical Constitution and Biological Activity. By W. A. Sexton, B.Sc., F.R.I.C. Foreword by Professor A. R. Todd, D.Sc., F.R.S. Industrial Chemistry Series. (Pp. 412. £2 15s.) London: E. and F. N. Spon.

This is a highly individual book. The author is a chemist and an authority on insecticides and herbicides, but his interests are wider than the study of chemotherapy. Briefly, he takes the whole problem of the relations which obtain between the structure and properties of chemical substances and the effects which they produce in living cells.

At first sight this book may appear to be a rather superficial survey, but the variety of topics it discusses constitutes its chief virtue. It does not pretend to be an authoritative treatise, nor is it merely a compilation of information gleaned from the literature; it is a well-informed and reflective discussion of those parts of the subject which have particularly interested the author. His outlook is that of a chemist, and he explains the biological effects of chemical substances in terms of interference with the intimate biochemical mechanisms of living cells. It is interesting that this viewpoint, so widely held to-day, usually involves the conclusion that drugs stimulate biological activities only indirectly, by inhibiting processes which normally hold those activities in check—e.g., by immobilizing enzymes or essential metabolites (cf. chapter II). Yet it is well known that some substances can accelerate biochemical processes by repairing a deficiency, as in "replacement therapy" (e.g., insulin or vitamin therapy). It is also conceivable that some drugs may accelerate or activate biochemical mechanisms directly, without inhibiting counterbalancing processes. "Local hormones" like acetylcholine and adrenaline may act in this way, and if so the difficult question arises whether drugs which imitate some or all of their effects are acting in the same way. Only drugs which are closely related in structure to the hormones would be expected to do so, but the possibility of such a direct mode of drug action is frequently overlooked. The book contains some misstatements (e.g., the formula of muscarine is wrongly given on p. 186 as that of betaine aldehyde), but these can be corrected in later editions.

H. R. ING.

SQUINT AND LATENT SQUINT

The Management of Binocular Imbalance. By Emanuel Krimsky, M.D. (Pp. 464; 200 illustrations. £3 3s.) London: Henry Kimpton. 1949.

This is a carefully compiled and well-illustrated work on squint and latent squint. The instruments and methods described in it for diagnosis and treatment will be in many instances unfamiliar to surgeons and orthoptists in this country. In general, the author places greater weight on objective than subjective methods of examination, whereas in the British Isles both methods are employed—the one being used to check the other.

The author throws some doubt on the desirability of giving corrective glasses to young children, and states that in hyperphoria the squint may be made worse. This view would be challenged by many ophthalmologists. He holds

that orthoptic exercises twice or three times a week are useless, and insists that they must be done daily. While this may be a counsel of perfection, it is impossible for mothers in this country who have no domestic help, are often working themselves, or who have a large family to look after in bad housing conditions; for her to attend more frequently and to give home exercises in satisfactory conditions is not always practicable. In any case, the good results obtained in our orthoptic clinics would belie such a gloomy view of their usefulness. The author says that it is not necessary to obtain complete straightness by operation in a case of convergence if glasses in addition will produce orthophoria, and that to operate a second time on eyes which are still squinting without glasses but are straight with is to invite divergence. This view again will not find general agreement. He is reticent on his treatment of divergence. Again, the treatment of paralytic squint is to trace the cause and cover the eye, the question of operation is tucked away elsewhere in the text.

These are but a few of the points which differ from the teaching in this country, and while the work may be read safely by surgeons and experienced orthoptists, it would not be suitable for candidates for the examinations of the Orthoptic Board. The index, very often a pointer to the usefulness of a book to the experienced reader, is full, but there are one or two omissions, such as "ocular torticollis," though this subject is discussed in the text.

J. D. M. CARDELL.

THESIS ON TROPHIC NERVES

Trophic Nerves. By R. Wyburn-Mason, M.D., M.R.C.P. (Pp. 1,083; 69 illustrations. £3 15s.) London: Henry Kimpton. 1950.

During the last century trophic nerves were considered to be of importance, but more recently their very existence has been questioned. Many lesions which were at one time regarded as "trophic" in origin have been considered to be due to injury or infection in areas deprived of normal sensation, or to be the result of disturbances in the vascular supply. In this volume Dr. Wyburn-Mason attempts not only to show that trophic nerves exist, but that these nerves and their connexions in the central nervous system are of fundamental importance in the co-ordination of the activity of all body tissues, and that many disease processes (including congenital growth abnormalities and a number of neurological and psychological disorders) are the result of alterations in their activity.

The author has obviously spent a great deal of time in assembling the evidence on which he bases his thesis, and the 930 pages of text are full of assorted information; but some of this, including clinical descriptions of many well-recognized diseases, seems hardly relevant to the main theme. There is unfortunately no final chapter in which the author's conclusions are integrated, and this is a defect of considerable importance in a work in which so revolutionary an idea is propounded.

J. W. ALDREN TURNER.

The Asthmatic Child, by Dr. G. F. Walker (pp. 19; 2s. 6d.; postage 2d.; Bristol: John Wright and Sons), is intended for the parents of asthmatic children. In the first two pages Dr. Walker gives general information on those factors commonly responsible for the development of asthma and sound general advice on how the children should be handled. The booklet includes a series of photographs demonstrating various breathing and relaxation exercises found to be of use in this condition with concise instructions on how they should be carried out. It is well produced and should serve the purpose of instructing and reassuring its readers.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Il Riso in Psicologia. By T. Senise. 2nd ed. (Pp. 542. No price.) Naples: Biblioteca Di. Il Cervello. 1950.

Untersuchungen über die Tuberkulose des Dünndarmes. By F. Bohm. (Pp. 71. M. 10.50.) Stuttgart: Georg Thieme. 1950.

I Congreso Hispano-Portugues de Farmacia. Pp. 1,036. No price.) Madrid: Real Academia de Farmacia. 1950.

The Deep Cervical Fascia. By E. S. Meyers, M.B., F.R.A.C.S. (Pp. 39. No price.) Brisbane: University of Queensland Press. 1950.

Social Medicine: : Its Derivations and Objectives. By I. Galdston, M.D. (Pp. 294. 22s.) New York: The Commonwealth Fund. London: Geoffrey Cumberlege. 1949.

Electroencephalography. Edited by D. Hill, M.B., F.R.C.P., and G. Parr, M.I.E.E. (Pp. 438. 78s.) London: Macdonald. 1950.

Essential Urology. By F. H. Colby, M.D. (Pp. 580. 61s. 6d.) London: Baillière, Tindall and Cox. 1950.

Annual Review of Medicine. Vol. 1. Edited by W. C. Cutting, M.D., and H. W. Newman, M.D. (Pp. 484. 48s.) London: H. K. Lewis. 1950.

Textbook of Endocrinology. Edited by R. H. Williams, M.D., and others. (Pp. 793. 50s.) London: Saunders. 1950.

A Primer for Diabetic Patients. By R. M. Wilder, M.D., Ph.D., F.A.C.P. 9th ed. (Pp. 200. 12s.) Philadelphia and London: Saunders. 1950.

A Manual of Cardiology. By T. J. Dry, M.A., M.B., Ch.B., M.S. 2nd ed. (Pp. 355. 25s.) Philadelphia and London: Saunders. 1950.

The Fundamentals of Personal Hygiene. By W. W. Krueger. 5th ed. (Pp. 284. 15s.) Philadelphia and London: Saunders. 1950.

Textbook of Biochemistry. By B. Harrow, Ph.D. 5th ed. (Pp. 609. 30s.) Philadelphia and London: Saunders. 1950.

Medical Gynecology. By J. C. Janney, M.D., F.A.C.S. 2nd ed. (Pp. 454. 32s. 6d.) Philadelphia and London: Saunders. 1950.

The Cytologic Diagnosis of Cancer. By the staff of the Vincent Memorial Laboratory of the Vincent Memorial Hospital. (Pp. 229. 33s.) Philadelphia and London: Saunders. 1950.

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FOLIC ACID ANTAGONISTS IN ACUTE LEUKAEMIA

The notion of biological antagonism, by which Woods[1] sought to explain the bacteriostatic effect of the sulphonamides, has provided an impetus for much pharmacological research. The folic acid antagonists are one of the most interesting of its progeny. When pteroylglutamic acid was synthesized[2] in 1946 its wide biological importance was already recognized. It was known to be an essential factor for the growth of many micro-organisms and to play an important part in animal metabolism. It had been found in high concentration in rapidly growing tumours[3]; it had been shown to accelerate the growth of mammary carcinoma in mice,[4] and to enhance the speed of the leukaemic process in man.[5] The deduction that such proliferative processes might be inhibited or arrested by deficiency of pteroylglutamic acid was obvious.

Attention was then turned to the synthesis of analogues of pteroylglutamic acid that might be expected to exert a biological antagonism to the parent substance. Some 40 of these have now been prepared,[6] those with the most powerful antagonistic action being aminopterin (4-amino-pteroylglutamic acid), a-methopterin (4-amino-N-10-methylpteroylglutamic acid), and amino-anfol (4-amino-pteroylaspartic acid). Their anti-folic-acid activity can be demonstrated by their inhibitory effect on the growth of *L. casei* and *Str. lactis R* in media containing pteroylglutamic acid, and by their inducing a "folic acid deficiency state" when administered to animals. Aminopterin and its analogues have been found to inhibit the growth of the Rous sarcoma in chickens[7] and of a transmissible sarcoma[8] and a mammary tumour[9] in mice. Reports on their effects on transmissible leukaemia in mice are less clear-cut: aminopterin has an irregular action, whereas a-methopterin significantly prolongs survival.[10]

In man the chief application of the folic acid antagonists has been in the treatment of the acute leukaemias. The first reports came from Meyer[11] in 1947, and since then several American haematologists have recorded their experiences.[12-18] In the opening pages of this issue of the *Journal* Dacie, Dresner, Mollin, and White, of the Postgraduate Medical School, report the first series of patients treated with aminopterin in this country. Their results are similar to those of American observers. Of 13 cases six were adults, and temporary remissions were obtained in one case of myeloblastic and one of monocytic leukaemia; in the remaining four patients, all with myeloblastic leukaemia, no improvement was noted. Temporary remission was observed in three cases of myeloblastic and four of acute lymphatic leukaemia in children. All writers are agreed that remission is never more than temporary, although Farber[13] has reported one case in which a remission lasted for 23 months; that the prospect of improvement is more favourable in children and in acute lymphatic leukaemia; and that remission is rare in monocytic leukaemia, while the myeloblastic type, in this respect, occupies an intermediate position. Remission may be accompanied by a complete return to normal of both the peripheral blood and the bone marrow, although a proportion of leukaemic cells commonly persists.

The dosage employed has been entirely empirical. Dacie and his colleagues, in general, gave 1 mg. daily to children and 1 to 3 mg. daily to adults, using the oral route and withdrawing the drug when a pronounced haematological effect or toxic symptoms were observed. Some American workers have attempted to give a maintenance dose of 0.5 to 1 mg. daily. Toxic symptoms are often severe and frequently necessitate interruption of treatment. They include ulcerative stomatitis, vomiting, diarrhoea, alopecia, an increased tendency to bleed, jaundice, and aplasia of the bone marrow. Whether all these effects, or indeed the therapeutic action of aminopterin, are to be attributed solely to its anti-folic-acid action is uncertain; there is evidence, from studies of the inhibition of bacterial growth, that the drug does not act as a simple competitive antagonist.[19]

At present it is fair to say that aminopterin and its analogues have more theoretical than practical importance in the treatment of acute leukaemia. These drugs will greatly increase the frequency of remission in this disease, but the remissions are only temporary. As Dacie and his associates point out, the effect of the drug

1 *Brit. J. exp. Path.*, 1940, **21**, 74.
2 Angier, R. B., and 15 others, *Science*, 1946, **103**, 667.
3 Pollack, M. A., Taylor, A., and Williams, R. J., *Univ. of Texas Publication*, No. 4237, 1942, 56; Loo, Y. H., and Williams, R. J., ibid., No. 4507, 1945, 123.
4 Lewisohn, R., Leuchtenberger, C., Leuchtenberger, R., and Keresztesy, J. C., *Science*, 1946, **104**, 436.
5 Editorial, *Blood*, 1948, **3**, 1057.
6 Messerschmitt, J., *Rev. d'Hematol.*, 1949, **4**, 194.
7 Little, P. A., Oleson, J. J., and SubbaRow, Y., *J. Lab. clin. Med.*, 1948, **33**, 1139.
8 Schoenbach, E. B., Goldin, A., Goldberg, B., and Ortega, L. G., *Cancer*, 1949, **2**, 57.
9 Higgins, G. M., and Woods, K. A., *Proc. Mayo Clin.*, 1949, **24**, 238.
10 Burchenal, J. H., Burchenal, J. R., Kushida, M. W., Johnston, S. F., and Williams, B. S., *Cancer*, 1949, **2**, 113.
11 *Trans. N.Y. Acad. Sci.*, 1948, **10**, 75.
12 Dameshek, W., *Blood*, 1949, **4**, 168.
13 Farber, S., Diamond, L. K., Mercer, R. D., Sylvester, R. F., and Wolff, J. A., *New Engl. J. Med.*, 1948, **238**, 787.
14 Meyer, L. M., Fink, H., Sawitsky, A., Rowen, M., and Ritz, N. D., *Amer. J. clin. Path.*, 1949, **19**, 119.
15 Pierce, M., and Alt, H., *Proc. cent. Soc. clin. Res.*, 1948, **21**, 89.
16 Strickney, J. M., Hagedorn, A. B., Mills, S. D., and Cooper, T., ibid., 1948, **21**, 31.
17 Wolman, I. J., Eglick, P., Dickstein, B., and Githens, J., *Penn. med. J.*, 1949, **52**, 474.
18 Sachs, M. S., Bradford, G. T., and Schoenbach, E. B., *Ann. intern. Med.*, 1950, **32**, 80.
19 Oleson, J. J., Hutchings, B. L., and Subba Row, Y., *J. biol. Chem.*, 1948, **175**, 359.

is to raise hopes which are dashed when the inevitable relapse occurs. The individual tragedies of acute leukaemia become even more poignant because they are protracted. Nevertheless a drug has been found which favourably influences the course of this disease, and, even if it is only a beginning, the importance of the discovery is evident.

HUMAN MILK

One of the major medical problems of the recent war, still incompletely solved, was to devise methods of studying the effects of dietary changes on the health of the nation. As a preliminary step investigations were made from time to time on the simpler question of deciding how far alterations in the national food supplies affected the intake of essential nutrients. These dietary surveys were supplemented in many instances by examinations of the levels of nutrients in the blood, urine, and other body fluids. Since it is generally recognized that the lactating mother is particularly vulnerable to nutritional deficiency, in having to provide both for her own needs and for those of her child, Dr. S. K. Kon and Mrs. E. H. Mawson decided to explore the possibility of using the composition of human milk as an indication of nutritional status. An account of their laborious investigations, carried out with the assistance of numerous helpers at the National Institute for Research in Dairying and elsewhere during the years 1941–5, has now been published.[1]

It was obviously desirable to collect specimens of milk from more than one place. The poor, working-class London district of Shoreditch was therefore chosen in contrast with the investigators' home area at Reading, a prosperous country town. From these two main centres, and from different hospitals in London and Oxford and a few volunteers not in hospital, over 2,000 specimens were collected. The constituents studied included vitamin A, carotenoids, vitamin B_1, riboflavin, ascorbic acid, fat, solids-not-fat, lactose, total nitrogen, calcium, phosphorus, and vitamin D. All these nutrients were seldom estimated in the same specimen of milk, and many more estimations were made of some nutrients than of others. From the start it was realized that for the satisfactory interpretation of the results it would be necessary to learn how the composition of the milk was influenced by factors other than the diet. The effects of the time of day, stage of lactation, milk yield, the age of the mother and her parity, were therefore investigated carefully. Serious difficulties had to be overcome in sampling, since the ideal procedure of collecting all the milk secreted over a period of 24 hours was rarely practicable. As a standard method the milk was expressed four to six hours after the last feed ; early or late collection caused serious irregularities in the fat content of the sample.

In fulfilling their original intention of establishing a relationship between the composition of the milk and that of the diet Dr. Kon and his colleagues can claim success on two important points. Analysis of milk from Reading women during 1941–2, when white bread was available, indicated a mean vitamin B_1 content of 14.7 μg. per 100 ml., whereas after the introduction of the national wheatmeal bread the level rose in 1944–5 to 18.3 μg. Increases were also observed in the yearly mean values for vitamin C between 1941 and 1945, and were presumably associated with an increased consumption of green vegetables, improved methods of cooking, and in later years the renewed importation of citrus fruit. Apart from these findings a great deal of information on the vitamin content of milk at different stages of lactation has been collected to supplement the data hitherto available from American sources.[2]

Many points of theoretical interest have also been noted. Thus after heavy dosing vitamin B_1 and riboflavin pass into the milk more readily than vitamins A and C. The main carotenoid pigment of the blood plasma is carotene, but in the milk fat lutein predominates, and lycopene and an unknown pigment accompany the small proportion of carotene. A perplexing question was presented by the consistently higher fat content of Reading milk, which averaged 4.78%, over Shoreditch milk, which averaged only 3.91%. Whether this difference was due to a greater fat consumption by the Reading women, or merely to an undetected error in sampling, could not be decided.

From a practical standpoint these studies may perhaps have their greatest value in emphasizing the effects of lactation on the vitamin supplies of the mother. Thus the daily secretion of vitamin A is usually about 1,100 i.u. This may appear small in relation to the daily allowance of 5,000 i.u., including carotene, which is recommended for a moderately active woman by the U.S.A. National Research Council, and which is increased to 8,000 i.u. for a lactating woman. It must be realized, however, that these allowances cover wide safety margins. In the experiment carried out for the Medical Research Council at Sheffield[3] a dose of 1,250 i.u. of preformed vitamin A sufficed to correct defective dark adaptation in an adult volunteer subjected to experimental deficiency of vitamin A. The lactating mother therefore secretes nearly enough vitamin A to cure deficiency in another person of about her own size. Similarly the daily secretion of 30 mg. of ascorbic acid would be sufficient to protect another adult from scurvy. As Kon remarks, the reserves available in the body,

[1] Kon, S. K., and Mawson, E. H., "Human Milk: Wartime Studies of Certain Vitamins and Other Constituents," No. 269, *Spec. Rep. Ser. med. Res. Coun. Lond.* H.M.S.O., price 2s., postage 2d. 1950.

[2] Macy, I. G., Williams, H. H., *et al.*, *Amer. J. Dis. Child.*, 1945, **70**, 135.

[3] Hume, E. M., and Krebs, H. A., *Spec. Rep. Ser. med. Res. Coun. Lond.* No. 264, 1949.

particularly of vitamin A, are substantial, and lactation by a mother receiving the ordinary diet should not cause serious depletion unless repeated at too frequent intervals. It seems highly desirable, however, to avoid even the risk of depletion, and the dietary intake of the mother should be increased at least by amounts equal to those which she secretes in her milk. From this point of view the safety margins allowed by the National Research Council seem not unreasonable.

SMOKING AND CANCER OF THE LUNG

Before 1920 cancer of the lung accounted in England and Wales for 1.5% of all cancer deaths in men; in 1947 it accounted for 19.7%. This dramatic increase has not been confined to this country, for similar changes have been reported from America, Australia, Switzerland, and Denmark. Whether they indicate a true increase in the prevalence of the disease or whether they are merely a reflection of improved diagnosis has not been determined, but most authorities agree with Kennaway and Kennaway[1] that the increase is likely to be real—at least in large part. The question that naturally arises is, What environmental changes have taken place which can have accounted for the increase? The use of tobacco is one obvious explanation. Tobacco products are certainly brought into contact with the bronchi, and the amount of tobacco smoked has steadily increased. But no one has been able to demonstrate experimentally any carcinogenic effect with tobacco. In these circumstances clinical evidence is most important, and it is surprising that so little is available. Müller[2] and Shrek and his collaborators[3] have produced suggestive figures, but until the papers by Wynder and Graham[4] and Levin, Goldstein, and Gerhardt[5] there had been no reports of large-scale planned investigations.

Wynder and Graham's work is the result of the co-operation of a large number of doctors in different parts of the U.S.A. Questionaries were filled in for 684 patients with histologically proved bronchial carcinoma (two-thirds of whom were personally interviewed by one of the authors). For comparison 780 male and 552 female patients from the general medical and surgical wards of three St. Louis hospitals were interviewed by non-medical assistants. Patients were asked to estimate how much tobacco they had smoked, on the average, over the last 20 years; in this way it was hoped to avoid the difficulties introduced by people changing their habits.

The results are striking. Of 605 male patients with epidermoid, undifferentiated, or histologically unclassified types of carcinoma only 1.3% were non-smokers—that is, had averaged less than one cigarette a day for the last 20 years—while 51.2% had smoked the equivalent of more than 20 cigarettes a day. In contrast, after adjustment had been made for age differences, 14.6% of the general medical and surgical male patients were estimated to be non-smokers and 19.1% to have smoked more than 20 a day. Twenty-five women with the same histological types of carcinoma provided a similar contrast with the female control series, but the small group of patients with bronchial adenocarcinoma gave a smoking history very like that of the non-cancer patients.

The results are open to the criticism that the control patients were interviewed by different examiners and were not drawn from the same parts of the U.S.A. as the cancer patients. Serious though this is, it would not appear to have biased the results, for the assistants who interviewed the general cases also interviewed a sub-group of the cancer patients, without knowing which they were, and obtained figures for this series closely similar to those obtained by the other workers.

Wynder and Graham further added the observations that patients with cancer of the lung smoked their tobacco disproportionately often in the form of cigarettes, that the sex ratio of the cancer patients corresponded roughly to the ratio of the long-term smoking habits of men and women, and that the increase in the sale of cigarettes in the U.S.A. approximately parallels the increase of lung carcinoma. They moderately conclude that the excessive and prolonged use of cigarettes "seems to be an important factor in the induction of bronchiogenic carcinoma."

Levin, Goldstein, and Gerhardt have reached the same conclusion. Their investigation was less elaborate but wider in its scope, and they were able to find a relationship between pipe smoking and cancer of the lip as well. These reports provide an important advance in knowledge. If they are confirmed it will still remain to trace the carcinogenic agent and to apply the lesson. Meanwhile strong support has been given to the existing financial reason for not smoking.

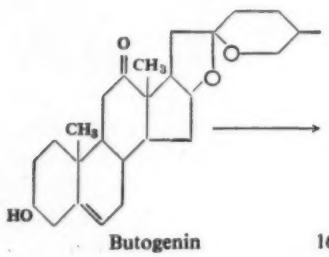
[1] *Brit. J. Cancer*, 1947, **1**, 260.
[2] *Z. Krebsforsch.*, 1939, **49**, 57.
[3] *Cancer Res.*, 1950, **10**, 49.
[4] *J. Amer. med. Ass.*, 1950, **143**, 329.
[5] Ibid., 1950, **143**, 336.

NEW SOURCES OF CORTISONE

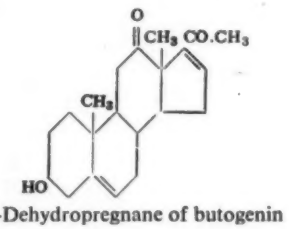
In the year which has elapsed since Hench and his colleagues[1] described the effect of cortisone on rheumatoid arthritis chemists have been active devising new methods of preparing this expensive drug, which at present is costing something like $100 an injection. There is no prospect of much reduction in price while ox-bile is used as raw material. From this is obtained desoxycholic acid, which is the starting-point in the 37-stage synthesis of cortisone. Ox-bile can never provide enough cortisone to meet the demand: it has been estimated that 12,500 tons of beef cattle are necessary to provide enough ox-bile for the preparation of a year's supply of cortisone for one patient with rheumatoid arthritis. Last autumn American chemists announced that the African vine, *Strophanthus sarmentosus*, contains a sterol, sarmentogenin, from which cortisone may be synthesized by a 17-stage process. But, as Dr. R. K. Callow shows in his article at p. 1484, no one yet knows just from what seed sarmentogenin has been isolated. The species of plant whose seeds yield sarmentogenin is apparently not *S. sarmentosus* after all. The botanists will no doubt soon identify the desired plant. Further investigations have shown that a number of plants native to North America contain sterols that might serve as sources of cortisone. A Mexican yam, *Dioscorea mexicana*, has been found to yield a steroidal sapogenin, butogenin, which

could be used as a starting-point for the synthesis.[2] Marker and Applezweig[3] have shown that many other plants containing related sapogenins flourish in North America : over 200 different species of more than 400 investigated have yielded steroidal sapogenins resembling butogenin in structure. Millions of tons of saponin-containing plants, which include aloes, cassavas, and yuccas, are already growing wild on the American continent, and in some cases yields as high as 10 kg. of sapogenin are obtainable from one ton of plant. There is thus an almost inexhaustible source of raw material available for the asking.

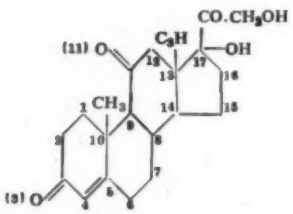
American workers have been exploring from this point of view the resources of their own continent, and have also sent expeditions to West and Central Africa. The Swiss and the British have been hot on the same trail. Dr. Callow gives a preliminary account of the expedition to Nigeria which he led for the Medical Research Council. From this Colony and Protectorate his small expedition returned with large quantities of seeds, dried plants, and crude extracts.



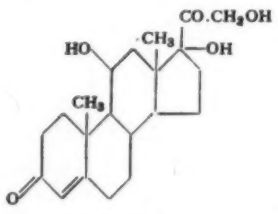
Butogenin



16-Dehydropregnane of butogenin



Cortisone
(17-hydroxy-11-dehydrocorticosterone)



Compound F
(17-hydroxycorticosterone)

Dr. Callow stresses that expeditions of this kind, while primarily engaged in the search for precursors of cortisone, may also bring to light plants botanically allied to *Strophanthus* which may contain useful steroids.

The steroidal sapogenins are more closely related to cortisone than is desoxycholic acid. Oxidation converts them into the corresponding 16-dehydropregnane. There is a double bond in the 16 position in the latter, and this affords an opportunity for the introduction of the 17-hydroxy group of cortisone[4] (see structural formulae). The presence of the double bond in the 16-dehydropregnanes affords a far simpler route for the construction of the side chain of cortisone than is afforded by the other known starting-points. Methods are also known for the conversion of a sterol containing a C-12 oxygen atom, which is present in the steroidal sapogenins, to one containing a C-11 oxygen, which is present in cortisone. The steroidal saponins may also be used as sources of the sex and adrenal-cortex hormones. According to a recent report[5] from the U.S.A. a method of using soya beans as raw material for cortisone appears promising. Workers at the Cleveland Clinic Foundation have obtained enzymes from the adrenal glands of cattle which have the power of converting a product known as stigmasterol, obtainable from soya beans, into "compound F," which differs from cortisone (compound E) by only one hydrogen atom in the 11 position, and which up to now has been obtainable only from animal glands. The clinical usefulness of the more recently available desoxycorticosteroids is still almost unexplored, and a new cheap source of raw material would give an impetus to further research in this field.

[1] *Proc. Mayo Clin.*, 1949, **24**, 181.
[2] See annotation in *British Medical Journal*, 1949, **2**, 974.
[3] *Chemical and Engineering News*, 1949, **27**, 3348.
[4] Fieser, L. F., and Fieser, M., *Natural Products Related to Phenanthrene*, 1949, New York.
[5] *New York Times*, April 22, 1950.

D.N.O.C. POISONING

Two fatal cases of poisoning by dinitro-ortho-cresol have been widely reported in the Press recently.[1] These two men were engaged in spraying D.N.O.C. in concentrated solution as a weed-killer. Apparently they were working long hours in very hot weather and had discarded their protective clothing. The diagnosis of the condition was not difficult, for there were symptoms of profuse sweating, thirst, and anxiety in men whose hands and wrists were stained with the yellow pigment. There is little that can be done in the way of treatment. Any hyperpyrexia may be treated, but usually death occurs without any great rise in temperature. The action of D.N.O.C., which farmers and agriculturists commonly call D.N.C., is probably more subtle than is usually recognized. The laboratory evidence that it interferes with phosphorylation is suggestive, but its relevance to the toxic action of D.N.O.C. has still to be worked out. At necropsy there is nothing beyond the staining of the skin to suggest the cause of death. The route of absorption may be partly through the skin, but where skin contamination is considerable it is likely that much more is absorbed through the lungs and alimentary tract, following inhalation of the dust or the spray, the ingestion of contaminated food, and the smoking of contaminated cigarettes.

The present trend in agriculture is to use many new organic insecticides and weed-killers. These compounds are of great value, but many of them are very toxic. In view of the world food shortage it is important that such insecticides and weed-killers should not be discredited because of carelessness in handling. Hunter[2] has pointed out clearly the hazards of spraying D.N.O.C., yet deaths such as the two recent ones are still reported. Protective clothing is usually intolerable in hot weather and is worn only during the occasional visits of a supervisor. Men still enter the spray cloud with the pump running to deal with faults in the nozzles ; they still mix the solutions with their bare hands ; they still have their meals without washing their hands and faces ; and they still drink water contaminated with D.N.O.C. The same difficulty arises with many industrial and agricultural hazards. It may be simple enough to design protective clothing and devise adequate

[1] *Daily Express*, June 8, 1950.
[2] *British Medical Journal*, 1950, **1**, 509.

rules and regulations; ensuring that the worker wears the clothing and obeys the rules is a very different and much more difficult problem.

A clear distinction should be made between the summer spraying of D.N.O.C. as a weed-killer and the use of D.N.O.C. as a winter wash on fruit trees. For the latter purpose it is used in dilute solution, at one-tenth of the concentration necessary for killing weeds, in cold weather, and during short working days. No cases of poisoning have yet been reported as a result of using D.N.O.C. as a winter wash, and it would be very unfortunate if it fell into disrepute because of its toxicity when used under entirely different circumstances. On the other hand, farmers will not readily give up the use of D.N.O.C. as a weed-killer, for it is the only compound that deals effectively with the red poppy in the wheat field.

The lesson to be learned is that each casualty has been the result of gross and avoidable contamination, and that subsequent treatment is of little avail. A full appreciation of the possible dangers of handling D.N.O.C. by those responsible for the spraying, with adequate supervision of the individual worker, should replace the issue of instructions that are ignored, the provision of protective clothing that is thrown aside, and the tendency to do no more than lip service to essential precautions. It is also significant that deaths have occurred only among the employees of firms engaged in contract spraying. It is obvious that men who are to be exposed daily to the same substance must be given working conditions that enable them to avoid excessive contact with the toxic materials. The casual user may well "get away with it" while using much less stringent precautions.

MUCOCUTANEOUS–OCULAR SYNDROMES

When Stevens and Johnson[1] reported in 1922 "a new eruptive fever associated with stomatitis and ophthalmia" they were unaware that Alibert and Bazin had described a similar condition almost exactly 100 years before. Stevens and Johnson thought the condition was a distinct disease of unknown aetiology and not a form of erythema multiforme. The general view to-day, however, is that this disorder is a severe and sometimes fatal form of the erythema multiforme of Hebra, in which the skin shows erythematous, haemorrhagic, purpuric, bullous, and necrotic lesions and the mucocutaneous surfaces of the mouth, genitalia, and conjunctivae are also involved to a varying extent. Most patients begin to recover after about three weeks, and the affection of the eyes is often the most serious feature. Partial or total blindness may result from the ocular manifestations, which vary from conjunctivitis to panophthalmitis.

A similar condition had been reported by other authors, in particular by Blair[2] and by Rendu,[3] a French military surgeon, who described "un syndrome caracterisé par l'inflammation simultanée de toutes les muqueuses externes coexistant avec une éruption varicelliforme puis purpurique des quatres membres." The designation "ectodermosis erosiva pluriorificialis" which was later given to the syndrome has never met with wide acceptance, possibly because of its tongue-twisting qualities, and the term "Stevens-Johnson syndrome" has been widely used, although often with the apologetic prefix "so-called." The Commission on Acute Respiratory Diseases[4] considered the eponym to be without historical justification, as was noted by Thomas[5] in his paper in the last issue of the *Journal*, reviewing the condition and describing six further cases. "Erythema multiforme mitis" and "erythema multiforme gravis" are terms that seem to describe adequately the different degrees of severity. It certainly seems desirable that the long-suffering student should be freed from the necessity of remembering too many eponyms. Some are misapplied, and others to-day comprise up to three hyphenated names. Haeberlin and Garrard[6] have listed 140 eponyms of dermatological significance for conditions many of which would be better classified on a histopathological or a descriptive clinical basis. Eponyms are best reserved as secondary synonyms for the use of those historically minded or well past the fact-cramming strain of their final examinations.

Klauder[7] pointed out that erythema multiforme may be a symptomatic cutaneous reaction to various agents (infections, drugs, sera, etc.), or it may be of the idiopathic or Hebra type, to-day widely believed to be of virus origin. This latter form may be mild, ocular, nasal, oral, pluriorificial, or of the severe mucocutaneous–ocular type. It is possible that the symptomatic form may also be of virus origin, the drug, infection, or other cause interfering with some biochemical process in the cells and so tilting the delicately balanced virus-host relationship sharply in favour of the virus.

Robinson and McCrumb[8] published recently a comprehensive review of Behcet's disease with its "triple symptom complex" of genital, oral, and ocular lesions; Reiter's disease with its urethritis, conjunctivitis, and arthritis; "Stevens-Johnson" disease; and ectodermosis erosiva pluriorificialis. They conclude that there are so many points of similarity between them that they are probably all variants of erythema multiforme exudativum, excepting possibly the so-called Reiter's disease. They suggest the term "mucocutaneous–ocular syndromes" to cover the whole group. Severe erythema multiforme must be borne in mind in the differential diagnosis of septicaemia, smallpox, the human form of foot-and-mouth disease, and some other acute infectious diseases. Stevens and Johnson's cases were both originally diagnosed as haemorrhagic measles. The condition is probably more common than the number of cases in the literature suggests, as many cases undoubtedly go unreported. Robinson[9] has recently described involution of the lesions in three to eight days in eight out of nine cases of erythema multiforme treated with aureomycin. Excellent results have also been reported in this country by Church[10] and by Lynas[11] in the gravis type of the syndrome, and aureomycin does seem to offer the best hopes at present for sufferers from this most severe malady.

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1 *Amer. J. Dis. Child.*, 1922, **24**, 526.
2 *Med. Rec.*, 1904, **65**, 729.
3 *Rev. gén. de Clin. et de Therap.*, 1916, **30**, 351.
4 *Arch. intern. Med.*, 1946, **78**, 687.
5 *British Medical Journal*, 1950, **1**, 1393.
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REFRESHER COURSE FOR GENERAL PRACTITIONERS

CONJUNCTIVITIS AND IRIDOCYCLITIS

BY

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When a patient seeks advice for an inflamed eye it is clearly important for his doctor to make a correct diagnosis as soon as possible, since upon this depends not only the treatment to be adopted but also the prevention of complications.

A careful examination is made in a good light, and the cornea should be studied with a corneal magnifier (loupe) if available. In hospital or private practice certain apparatus is available to the oculist (e.g., a slit-lamp or a special inspection lamp) which may give information not obtainable without its use, but in most cases a correct diagnosis should be reached without such aid if attention is paid to certain clinical features which vary according to the cause of the trouble. Below is a table showing the points of difference between the three common causes of an acutely inflamed eye—namely, acute conjunctivitis, acute iritis, and acute glaucoma.

Points of Difference Between Acute Conjunctivitis, Acute Iritis, and Acute Glaucoma

	Conjunctivitis	Iritis	Glaucoma
Age ..	Any	Not children	Elderly
Sex ..	Either	Either	Females more common
Unilateral or bilateral	Either	Either	Unilateral, but the other eye often develops the disease
Symptoms	Grittiness and pain accompanied by discharge. Vision not impaired except by flecks of mucus which can be blinked away, or by the lid margins adhering as a result of dried secretion. (N.B. The presence of a corneal ulcer causes more pain, intolerance of light, and impairment of sight)	Severe pain in and around the eye. Vision is impaired in varying amounts; may be considerable	Intense pain, radiating to the forehead. The pain can be severe enough to cause vomiting. Vision is seriously impaired
Signs ..	A clear cornea, active pupils, and a healthy-looking iris. The conjunctiva is intensely injected, and scarlet in colour; this colour tends to fade towards the cornea. If the conjunctiva is moved by gentle pressure through the lid the injected vessels move with it	The conjunctiva is injected, there is a purple flush round the limbus (circumcorneal injection), which is in contrast to the peripheral scarlet of conjunctivitis. The cornea may be clear, but with a loupe small grey spots may be made out on the posterior surface (K.P.). There may be exudate in the anterior chamber; adhesions between iris and lens (synechiae) may have formed. The iris is swollen and "muddy" and is less bright in colour than its fellow. New blood vessels may be visible in the stroma	The conjunctiva is injected in varying degrees (may be slight in the very old). The cornea is misty, due to oedema, making details of the iris difficult to see. The fundus is not visible for the same reason
Discharge ..	Watery, mucopurulent, or purulent	Watery	Negligible
Tension ..	Normal	Normal	Greatly raised
Pupil ..	Normal in size and reactions	Constricted; sluggish in reaction	Semidilated, oval, inactive

By careful consideration of the data included above a general practitioner should be able to decide upon his diagnosis without any more aid than a good light and a corneal loupe.

Acute Infective Conjunctivitis

Signs and Symptoms.—These are indicated above. Discharge may be mucopurulent or purulent. Before any treatment is started a bacteriological examination is advisable if it is easily available, but treatment should not be delayed.

A. Local Treatment

The eye is gently irrigated with lotion. It may be necessary, before the eye can be opened, to bathe off dried crusts of secretion by means of cotton-wool pledgets soaked in lotion. There are a number of eye lotions in use. The important thing to remember is that it is not possible to use an antiseptic in a strength sufficient to have antiseptic value on a delicate tissue like the conjunctiva or the corneal epithelium. Therefore any lotion used merely acts as a diluent and flushes away products of inflammation; thus it does not matter greatly what lotion is recommended (except in conjunctivitis from chemical burns). The following are in common use: normal saline, hydrarg. perchlor. 1/10,000, hydrarg. oxycyanid. 1/8,000, sod. bicarb. 2%, acid. boric. 2% (5 gr. to 1 oz. equals 1% approximately).

Irrigation is carried out with an undine or by means of a dropper, which should be sterile. The patient should be lying down and his head turned to the affected side to prevent infected fluid from reaching the other eye. It is not easy to irrigate one's own eye, so, if possible, someone who has access to the patient should be shown how to do it.

On completion of the irrigation penicillin ointment (oculentum penicillin, 2,000 units per gramme) is placed inside the lower fornix and along the lid margins. This is conveniently done by means of a small glass rod, and again someone with the patient should be instructed in the method, which is to place the glass rod with the ointment in the lower fornix, get the patient to squeeze the lids together, and then gently withdraw the rod sideways while the lids are still together. The eye should on no account be bandaged. Dark glasses with protective sidepieces or, failing this, a lint flap or soft eye-shade may be worn. The patient should be instructed to avoid draughts, strong wind, smoky atmospheres, and any external irritant. If practicable it is advisable to rest the good eye for a day or two in order to prevent the affected eye from being used. The patient must be instructed not to employ handkerchiefs, towels, etc., when treating the eye, but to use cotton-wool and burn it after use. The risk of infecting the good eye and the eyes of others must be explained. Further treatment consists of:

1. Irrigation night and morning, or more often, depending on the amount of discharge and the severity of the attack.

2. The use of oculentum penicillin at intervals of four to six hours by day. The eye must be kept under the

effect of penicillin all the time. As the potency of penicillin ointment lasts about four to six hours in the conjunctival sac it is clear that renewal of it should take place at about this interval. It is of little value to prescribe penicillin in the eye for any inflammation once a day or twice a day; it must be used four- to six-hourly. Furthermore, I believe that if penicillin has not done its work after seven days it is useless to continue with it, and something else should be tried. Penicillin drops may be used, 1,000 or 2,500 units per ml., but their potency lasts for less time than that of the oculentum, and liquids so easily escape from an inflamed eye that drops are much less effective. Drops are indicated for prophylactic purposes or in very severe cases where there is much pus. (See below, ophthalmia neonatorum.) If any further treatment is required after seven days penicillin is replaced by sulphacetamide—in the form of ung. sulphacetamidi 20% or guttae sulphacetamidi 20%. In severe cases in which a secondary iritis might develop or in which there is any suspicion of corneal involvement guttae atropinae 1% should be instilled daily.

B. General Treatment

Systemic injections of penicillin 200,000 units twice daily should be used only if the cause is thought to be due to some endogenous infection, or if the case fails to progress quickly. Similarly with the sulpha drugs (by mouth). It should not be necessary to employ the latter unless the inflammation is caused by a penicillin-resistant organism, and I regard it as unnecessary to use both together in most cases. Obviously the patient's general condition must be kept as good as possible, and his adviser will determine from the severity of the case whether he is to be confined. Fresh air is to be encouraged. Some varieties of conjunctivitis require some modification in treatment:

Ophthalmia Neonatorum.—Since the advent of penicillin this disease has become much less dangerous to sight. The treatment adopted (Sorsby) is as follows: oral treatment (sulphadimidine 0.5 g. followed by 0.25 g. every six hours) is combined with local penicillin drops (10,000 units per ml. at intervals of one minute for half an hour and then less often as the discharge lessens). Results are quite dramatic compared with the "pre-penicillin period." These cases should be treated in hospital.

Acute Conjunctivitis from Dacryocystitis.—The lacrimal sac is repeatedly emptied by pressure over the internal palpebral ligament and the eye then irrigated in the ordinary way. As soon as the patient can tolerate it the sac is syringed and penicillin (1,000 units per ml.) is left in it. This is repeated when necessary.

Angular Conjunctivitis.—That part of the conjunctiva exposed by the palpebral fissure is most often involved. The disease is caused by the Morax–Axenfeld diplobacillus, and is cured by the application of zinc drops, ½ gr. or 1 gr. (32 or 65 mg.) to the ounce (28 ml.), which may well be combined with sulphacetamide 20% to counteract secondary infection.

Membranous Conjunctivitis.—The conjunctival sac is immediately examined bacteriologically for diphtheria, and the appropriate treatment undertaken if this is positive. The membrane is stripped off with forceps.

Purulent (Gonococcal) Conjunctivitis.—Treat as ophthalmia neonatorum, see above. These cases should always be treated in hospital.

Acute Non-infective Conjunctivitis

This type is mostly due to injury or corrosive burns. The cause of the trouble is obvious from the history.

Treatment

Foreign bodies must be removed as soon as possible. Examination of the under surface of the upper lid and the upper fornix must never be neglected.

Burns.—If these are caused by acid the eye should be irrigated with an alkaline lotion (lotio sod. bicarb. 2%), and vice versa (lotio acid. boric.). There is always a danger of the raw surfaces adhering, a condition called symblepharon, and this later gives rise to considerable limitation of movement of the globe, with diplopia. To prevent this the fornices are liberally lubricated with guttae parolein or castor oil, and sterile petroleum jelly is placed therein. Daily a glass rod is passed along both fornices to break down any adhesions that may have formed.

Lime Burns.—Any lime remaining *in situ* is carefully removed. The eye is irrigated with 10% ammonium tartrate and the conjunctival sac kept lubricated with "paroleine" to prevent adhesions. All except very slight cases of lime or other caustic burns should be treated in hospital because of the danger of corneal damage

Special Types of Conjunctivitis

1. *Phlyctenular.*—In this disease nodules appear on the conjunctiva or cornea, to which a leash of blood vessels run. It is a common disease of childhood, and there appears to be a very definite connexion between phlyctenular disease and sensitivity to tuberculous toxin. General treatment is therefore important—fresh air, nourishing food, and sunlight should be sought. Local treatment is relatively unimportant unless the cornea is affected, because phlyctenules soon disappear.

2. *Associated with Skin Diseases.*—The importance of such cases is that the conjunctivitis is always secondary, and will not be cured unless the skin disease is cured. Most important are rosacea (in which the cornea is nearly always affected) and conjunctivitis associated with seborrhoea capitis or acne vulgaris. Treatment of the eyes is therefore palliative.

3. *Allergic.*—Characterized by sudden onset and recession, and by being bilateral. Eosinophil cells may be found in a conjunctival smear. In a suspected case it will be necessary to subject the patient to protein-sensitivity tests to find out what he or she is to avoid. Local treatment consists of "antistin-privine" drops (1%) frequently, and "benadryl" by mouth may be justified.

4. *Spring Catarrh.*—This has a seasonal incidence and attacks young people. It is probably allergic. The common form affects the eyelids, in which large follicles "like paving stones" appear. There is a milky secretion. The bulbar form affects the limbus area. Eosinophils are found in a conjunctival smear. The patient complains of a great deal of itching. Treatment is palliative. The antihistamine drugs are used. Trachoma, conjunctival tuberculosis, syphilis, and other diseases are now uncommon, and cannot be considered here.

Chronic Conjunctivitis

The clinical appearances vary considerably. The eye may be severely injected, the conjunctiva swollen and "velvety" in appearance, the lower lids tending to evert and expose the mucous surface, thus adding to the irritation. On the other hand, all that is visible may be a mild degree of conjunctival hyperaemia, or a little epiphora or sticky discharge. In a like way the symptoms can be out of proportion to the signs.

Points Worth Remembering

1. Cases can be made worse and the inflammation may be prolonged by too much treatment—especially by astringents.

2. Many cases are due to some constitutional factor—metabolic (e.g., gout), general debility—poor living conditions, and skin diseases (many of which are in themselves metabolic—e.g., rosacea). It is necessary to treat these underlying factors as well as the eyes.

3. Allergy may be a cause. In such cases there is often an allergic history or family history. Locally the suggestive signs are a very sudden onset (bilateral) and a very sudden cessation of the attack, with frequent recurrences. In women, face powder, mascara, and other cosmetic preparations are sometimes responsible. Most non-allergic cases subside very slowly and reluctantly.

4. In a unilateral case great care must be taken to exclude foreign bodies, misplaced or ingrowing eyelash, dacryocystitis, intranasal infection, conjunctival concretions protruding above the epithelial surface, and conjunctivitis artifacta. In the last-named the type of patient may give a clue, and the inflammation is almost always in the lower fornix. Self-inflicted conjunctivitis is usually produced to escape work or some distasteful duty, and so long as the possibility of it is remembered it is usually not difficult to recognize it.

5. Refractive errors may play a part, and should be investigated.

Treatment of Chronic Conjunctivitis

Mild astringents are used in the form of drops. These must not be prolonged indefinitely. There is usually very little discharge, so that lotions are often unnecessary. At the outset the surgeon may paint the lids with 25% or 50% argyrol. This is done quite firmly (under amethocaine hydrochloride) and the excess silver washed out. For home use the patient is given guttae zinc. sulph. ¼ gr. (16 mg.) to the ounce (28 ml.); or Crooke's collosal argentum, twice daily. I have found the following effective: zinc sulphate ¼ gr. (8 mg.), sol. adrenalin. 1/1,000 30 m. (1.8 ml.), sol. sulphacetamidi 10%. If allergy is suspected, use guttae antistin-privine 1% three times daily. Some patients need a placebo. Guttae phenolaine is a soothing preparation. The great thing is to prevent the patient becoming a permanent user of drops.

It is as well to tell the patient that chronic conjunctivitis is not easy to cure; a lot depends on general health, surroundings, and finding and eliminating the cause. It is the responsibility of the doctor to be sure that everything is done to eliminate any factors which may be contributing to the condition. It is worth remembering that not all hyperaemic conjunctivae cause symptoms. If the patient is not complaining of gritty eyes or soreness he is best left alone.

Iridocyclitis

For our purpose iritis and iridocyclitis can be considered together. The presence of small grey spots (keratitis punctata, or K.P.) on the posterior corneal surface indicates ciliary activity. Chronic cyclitis—a most insidious and resistant disease—may occur for a long time without any obvious iris inflammation, but sooner or later this takes place; clinically, however, it may only show, in later stages, as iris atrophy.

The end-results of iridocyclitis can have a most serious effect upon vision. Some of these can be prevented by early treatment, particularly adhesions between the iris and lens capsule (posterior synechiae). Such adhesions are caused by the organization of fibrin into fibrous tissue, and are produced by the formation of fibrin from the vessels of the inflamed iris. When they become fibrous, adhesions are very tough, and often cannot be broken down. Dilatation of the pupil is restricted and irregular; circulation of the aqueous may be interfered with (if the adhesions are extensive), with resultant iris bombé and secondary glaucoma; the transparency of the lens capsule, and later the lens, may be impaired; and finally, synechiae are said to predispose to recurrent attacks of inflammation. (This is probably fallacious.)

The object of immediate treatment is to prevent the formation of synechiae by getting the pupil margin as far away from the lens capsule as possible. For this we use a mydriatic—atropine—and it is clear that a correct diagnosis will greatly facilitate the prevention of adhesions.

Acute Iridocyclitis

The signs and symptoms of acute iridocyclitis have been briefly considered under "differential diagnosis." The treatment is conveniently considered as local and general.

Local Treatment

Some form of mydriatic is instilled as soon as the diagnosis is made. I believe it to be best to use atropine ointment 1% (2% if adhesions have begun) thrice daily. Atropine drops are in common use, but so easily are they spilt over the lids, diluted by the tears, or dabbed off that the drug does not remain *in situ* long enough to be absorbed in quantity. Some form of heat is employed for the relief of pain and to stimulate the blood flow. This can be given as moist heat in the form of hot bathings, or dry heat by means of a Maddox heater. Heat is also used in the form of diathermy (500 mA for five minutes), but this may not be available except in hospital. Dark glasses are worn as a protection against light; a bandage is unnecessary. Relief from vascular engorgement may be obtained by applying leeches to the temple.

Should adhesions form in spite of early application of atropine it may be possible to break them down by means of a more powerful mydriatic injected subconjunctivally. This is called "mydricaine," and it is a combination of atropine 1/60 gr. (1 mg.), cocaine 1/10 gr. (6.5 mg.), adrenaline 1/600 gr. (0.1 mg.), sodium chloride 1/80 gr. (0.7 mg.), and chloretone 1/120 gr. (0.54 mg.), in 5 minims (0.3 ml.) of sterile water. Five minims of this is injected near the limbus, opposite the offending synechiae. Sometimes the patient may develop sensitivity to the local application of atropine. This shows itself as a local reaction: the skin of the eyelid becomes very dry and puffy, the whole of the affected side of the face may become considerably swollen, there is a great deal of itching, and the eye itself becomes more injected. Should this condition arise, atropine must be stopped immediately and other mydriatics employed. We can use hyoscine hydrobromide 1% or duboisine sulphate 1%. A synthetic preparation "lachesine" 2%, has recently become available, and is useful in that it does not give rise to allergic reactions, but it is a good deal less potent than atropine.

Surgical procedures comprise iridectomy, dividing synechiae, iridotomy to produce an artificial pupil, etc., details of which are not given here.

General Treatment

Some oculists advocate protein-shock therapy in early stages of acute attacks. There is not universal agreement about the efficacy of this form of treatment. It is difficult to assess the value of it, because there is no control with

which to compare. Shock therapy is conveniently given by means of an intravenous injection of typhoid vaccine (15,000,000 units), which can be repeated with slightly higher dosage two or three times a week, provided the general reaction is not too severe. For the relief of pain in the acute attack, aspirin, phenobarbitone, "veganin," etc., are in general use. In rare cases of acute pain morphine may be needed.

Specific treatment may be indicated. This depends on the cause of the attack. Therefore as soon as possible after immediate local treatment has begun investigations should be made to try to bring to light any relevant aetiological factor. It must be admitted, however, that, despite the advance made in modern medicine and diagnostic technique, the majority of cases of iritis remain unexplained. Briefly, the following diagnostic methods are used : (*a*) A careful history. This may give a pointer to the cause, and in many cases the patient's doctor can assist with his knowledge of previous illnesses. (*b*) Blood examination for Wassermann and Kahn reactions, gonococcal infection, etc. (*c*) Focal sepsis must be eliminated, and this involves investigation of sinuses, teeth, etc. In women, gynaecological causes must be excluded. (*d*) Radiographs to exclude sarcoidosis or tubercle, either healed or active. (*e*) Urine examination, especially for sugar.

Aetiology

The following are the generally accepted causes of inflammation of the uveal tract :

Primary Causes.—(*a*) Syphilis ; (*b*) gonorrhoea ; (*c*) tuberculosis ; (*d*) focal sepsis ; (*e*) herpes zoster ; (*f*) metabolic (gout, diabetes) ; (*g*) allergy ; (*h*) uveoparotitis ; (*i*) sarcoid ; (*j*) undulant fever.

Secondary Causes.—(*a*) Injury ; (*b*) corneal inflammation (e.g., herpes) ; (*c*) post-operative (e.g., endophthalmitis phaco-anaphylactica).

Primary iridocyclitis is an endogenous reaction. The clinical features of individual types sometimes have diagnostic value, and will be briefly mentioned. Any relevant special treatment will also be indicated.

(*a*) *Syphilis.*—This is probably a less frequent cause than heretofore, owing to earlier diagnosis and treatment of syphilis itself. Some years ago it was said to account for 25% of cases of iritis, but the figure is a good deal lower now. Syphilitic iridocyclitis occurs in two forms—a "plastic" and a "nodular or gummatous" form. The plastic form appears in secondary syphilis, accompanies the skin rashes, and usually occurs between three and twelve months of infection. It is sometimes characterized by excessive formation of fibrinous exudate, but there may be no local distinguishing features. The "gummatous" form occurs in late secondary or early tertiary syphilis, and is distinguished by usually multiple yellowish nodules forming at the pupil margin. Special treatment is of course that for syphilis, the details of which need not be repeated here. It will suffice to mention that iodides may have a beneficial effect on the rapid absorption of nodules in the gummatous type. A mild iritis occurs in congenital syphilis in conjunction with interstitial keratitis.

(*b*) *Gonococcal.*—Ninety-six per cent. of cases are found in men. There is nearly always an accompanying arthritis or a history of joint pains (usually the knee or ankle), and the primary urethritis has probably subsided. Recurrent attacks are common, and may arise when no evidence of the original attack of gonorrhoea is present. Thus the cause may be difficult to find unless a truthful history is obtained. The local feature is that of a gelatinous exudate which is rather greenish in colour and excessive. Special treatment in chronic or recurrent cases is prostatic massage. A gonococcal vaccine is sometimes advocated.

(*c*) *Tuberculosis.*—This usually occurs in children or young adults. The inflammatory reaction is often less acute in tuberculous cases. Nodules may occur rather similar to those of syphilis. K.P. tends to be rather coarse and large, and may easily be visible to the naked eye. Special treatment consists of the usual fresh-air-and-diet regime. The patient should live in the country. Tuberculin injections, beginning with very small doses, can be effective, but, because of the difficulty of assessing the correct dosage, should be given by experts. In ocular tuberculosis large doses of vitamin D (calciferol) are worth a trial—100,000 i.u. daily given in tablet form up to a total of 18 to 33 million i.u.

(*d*) *Focal Infection.*—There are no local distinguishing features except that often the case takes a more subacute to chronic form. K.P. is produced in crops and vitreous opacities are excessive. Treatment consists in eliminating the focus if possible. Sulphanilamide therapy or systemic penicillin might be useful for the focal infection, but has not any local ocular effect. Autogenous vaccines are used and sometimes seem to modify an attack.

(*e*) *Herpes.*—Iritis occurs in association with herpes zoster, usually when the cornea is involved, but it may occur independently. It may also arise in conjunction with herpetic keratitis. A virus infection is generally accepted now as the cause. No special treatment is indicated here.

(*f*) *Metabolic.*—(1) *Diabetes.* There is a tendency for a large number of visible blood vessels to form on the iris, producing a condition known as rubeosis, which is pathognomonic. Hyphaemia is common. General treatment for diabetes is usually already in operation, as iritis is not likely to be an early sign. (2) *Gout.* This disease itself is much less frequent than it was ; iritis has been freely attributed to gout in the past, and probably in many cases erroneously. However, a gouty iritis does occur ; it is often associated with episcleritis. There is very considerable pain, and the ocular tension is often raised. General investigations—blood uric acid, radiography of joints (if any are affected)—should be carried out. Any positive evidence will entail careful treatment of the underlying metabolic disorder.

(*g*) *Allergy.*—The subject of allergy is vast, and I believe it to be a very important factor in eye disease, but it can only be briefly mentioned here. There is no doubt that the uveal tissue develops hypersensitivity. For example, recurrent attacks of iridocyclitis occur long after the original cause has been dispersed ; this suggests a reaction to a stimulus which would not have been effective prior to the original attack. An allergic cause is difficult to prove and more difficult to isolate, but in a suspected case it is justifiable to try the effect of antihistamine drugs—benadryl (50 mg. thrice daily) or antistin (100 mg. twice daily).

(*h*) *Uveoparotitis.*—This is an unusual form of iridocyclitis associated with enlargement of the glands and sometimes with cranial nerve palsy. Tuberculosis is usually accepted as the underlying cause. There is no specific treatment.

(*i*) *Boeck's Sarcoid* (*Benign Lymphogranulomatosis*).—This disease is one in which nodules appear in the skin, lungs (particularly the hilar region), lymphatic system and conjunctiva, and other internal organs. Iridocyclitis is not uncommon in the disease and is characterized by the formation of iritis nodules. Uveoparotitis is considered by some authorities to be a variety of benign lymphogranulomatosis.

(*j*) *Undulant Fever.*—Chronic iridocyclitis is associated with this illness. No specific treatment is indicated.

Chronic Iridocyclitis

There is a form of uveal inflammation which manifests itself in a manner likely to remain unnoticed by the patient for some time. The first symptom is diminution of vision, or maybe rapid increase in presbyopia. On examination only very fine vitreous opacities and fine K.P. are found. With a slit-lamp it is possible to see cells circulating in the aqueous. There is probably no circumcorneal injection (ciliary flush).

In spite of local treatment the disease tends to remain active; very often a secondary glaucoma supervenes, and this is a most serious matter. Very few of such cases resolve, and the eye is usually lost after a period of relapses. Little or nothing is known about this disease. It is attributed to such possibilities as septic absorption, allergic reaction, and tuberculosis—but rarely is anything definite found, elimination of which cures the local disease. Treatment therefore consists of atropine, rest, and complete overhaul; and if secondary glaucoma occurs operative treatment may become urgent.

EXPEDITION TO NIGERIA

M.R.C. SEARCH FOR TROPICAL PLANTS

BY

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In November, 1949, an expedition was sent by the Medical Research Council to Nigeria to investigate certain tropical plants as possible sources of raw materials for the preparation of cortisone. The members of the expedition have recently returned, and, although evaluation of results must wait upon the completion of detailed laboratory investigation, some account of the background of their work and of its progress can be given.

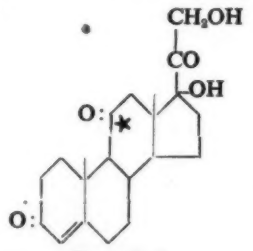
The expedition, under the title of the Medical Research Council Medicinal Plants Survey, consisted of myself and a technical assistant, Mr. W. Read, from the National Institute for Medical Research, with a botanist, Mr. R. D. Meikle, of the Royal Botanic Gardens. During our stay in Nigeria we had our headquarters in University College, Ibadan, and grateful acknowledgment is made of the invitation from the Principal, Dr. Kenneth Mellanby, and of the laboratory facilities which were made available by Professor R. J. McIlroy and Professor F. W. Sansome, in the Chemistry and Botany Departments respectively.

FIG. 1.—Bush resthouse at Kagara. The M.R.C. expedition on tour.

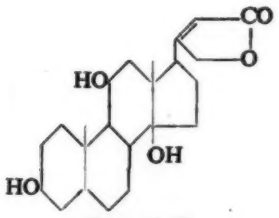
Origin of the Expedition

To explain the need for the expedition it is necessary to recall the sensational announcements, made just over a year ago, of the therapeutic activity of cortisone ("Compound E," 11-dehydro-17-hydroxycorticosterone; Formula I) in rheumatoid arthritis, and the fantastic discrepancy between the quantity of this compound which could be made available and the potential demand for its use. Although the compound is present in extracts of adrenal cortex, to obtain any considerable amount from this source is plainly impossible. A complicated many-stage synthesis from bile acids is known but is expensive, and the United States journalists have emphasized sufficiently the almost astronomical number of cattle which would be required for the maintenance of a single patient.

Synthetic routes to the adrenocortical hormones have been, and are being, busily explored; but a major difficulty is the introduction of the oxygen atom in position 11 in the steroid ring system (* in Formula I). This structure seems to be essential for the required type of biological activity. Were it possible to begin a partial synthesis



Formula I.



Formula II.

from a natural product with this bit of the molecule "ready made," the problem would be immensely easier. Attention was early directed to sarmentogenin, one of the group of heart poisons, the constitution of which, with an 11-hydroxyl group (Formula II), had recently been proved by Katz, in Switzerland.

Sarmentogenin was believed to occur in the seeds of *Strophanthus sarmentosus* P.D.C., a climbing plant of West Africa, and United States journalists rapidly sketched visions of vast areas of Texas planted with crops which would supply the rheumatoid arthritics of the world. The bubble burst when two of Professor Reichstein's colleagues collected in West Africa authentic seeds of *S. sarmentosus*, and it was shown that they contained little or no sarmentogenin but mainly a new heart poison, sarverogenin, the constitution of which is still undetermined. The origin of sarmentogenin now presented a fascinating scientific mystery.

Sarmentogenin had been isolated by three groups of workers, on each occasion from commercial samples of seed coming on to the market described as seeds of *Strophanthus hispidus*. In each instance pharmacognostic examination indicated that the seeds were not those of *S. hispidus*, but in general corresponded most closely in properties, particularly in colour reaction, with seeds of *S. sarmentosus*. If now, from the Swiss results, the source of sarmentogenin were not *S. sarmentosus*, what seed

could it be? It was a seed which occasionally came on the market in large quantity. Could it be the seed of a botanically unrecognized species, of a species hitherto considered rare, of a strain or variant of either *S. hispidus* or *S. sarmentosus*, or a seed used as an adulterant by native collectors? Precise information, even of the distribution and frequency of occurrence of *S. sarmentosus*, could not be obtained in the United Kingdom, and the Medical Research Council, at short notice, decided to organize this expedition. Expeditions have also been sent from the United States and from Switzerland to West and Central Africa. No results of the American work have been published, but from Professor Reichstein's laboratories a series of papers is appearing in which the systematic examination, one by one, of the African species of *Strophanthus* is being described—so far without sarmentogenin being found except as a minor constituent.

FIG. 2.—Near Zaria, N. Nigeria. An African forest guard with blossoms of *S. sarmentosus*.

An Important Objective

A second, and potentially perhaps more important, object of the Medical Research Council expedition was to investigate plants botanically allied to *Strophanthus* which might contain useful steroids, not necessarily heart poisons. Plants of the Apocynaceae, the family which includes the genus *Strophanthus*, and the Asclepiadaceae were given special attention, and the Director of Research of the Colonial Products Research Council was able to suggest many other plants, incompletely investigated, which deserved further chemical analysis from this aspect. This part of the research scheme, which is being carried out in collaboration with Dr. J. W. Cornforth, will in due course undoubtedly yield results of scientific interest, and perhaps also of practical importance, but the subject is not yet sufficiently developed for anticipatory discussion.

FIG. 3.—*Strophanthus sarmentosus*: an unripe pod.

The botanical work by Mr. Meikle was of prime importance in the unambiguous identification of the species collected. Moreover, his observations have added a great deal to our knowledge of the distribution and habitats within Nigeria of *Strophanthus* and other species. Botanically, the Nigerian flora is but partially known and recorded as lists of species from scattered localities. Questions of distribution, habitat, and oecology—all that lies beyond herbarium botany—await investigation.

In its botanical exploration and collecting the expedition had the invaluable help of officers of the Agriculture and Forestry Departments with their local knowledge or guidance to sources of information. *Strophanthus* is neither a crop nor a forest product, and in this actively—even feverishly—developing country these officers are busy men. As one put it, "Our people are too busy to sit under bushes waiting for pods to ripen, but we shall be delighted if you come out to do that job, and we will give you all the help we can." The Emir of Katsina, awake to the potential importance of a new natural product, instructed district and village heads to organize collections of "kwankwani," and an almost overwhelming quantity of 10,500 pods of *S. sarmentosus* was obtained within four days. Elsewhere, the expedition visited villages of the primitive "pagan" tribes and gathered the crops from their bushes cultivated for the hunters' supply of arrow poison.

Potentialities for Research

These occupations were by no means sedentary: the botanist and the chemist covered over 9,000 miles by road in the course of their survey and, incidentally to their main task, had a great opportunity of appreciating the wealth of scientific and medical subjects calling for research in West Africa. The difficulties are to find housing, equipment, and money for work to be done by people in the country with knowledge of conditions there. Nigeria is a healthy region for Europeans now that specifics against malaria are available, but the high temperatures and humidities, particularly in the south, are trying, and exasperations and frustrations are magnified. Nevertheless scientific work is beginning—for instance, the recently organized scheme for investigation of Nigerian medicinal plants and native medicines at University College, Ibadan—and the African, with the heavy handicap of lack of any tradition of science, and sometimes even literacy, is demanding and obtaining European education, and efforts are being made to attract him to technical and scientific work for his country.

In Nigeria, the expedition's programme of laboratory work was subordinated to collecting, with the result that a large quantity of material, in the form of seeds and dried plants or crude extracts, which was brought back has now to be examined more closely. This will take time, and, though if all goes well the scientific results will emerge in due course, it must not be thought that a solution of the problem of getting a precursor of cortisone is just round the corner. Even if a plant rich in such a substance be found, its cultivation and the methods of extracting the raw material will need further long research.

A circular from the Ministry of Education discussing the education of girls before they start nursing courses takes the view that the best preparation that most students can have for nursing is a broad general education at school, preferably up to the age of 18. On the other hand, some secondary schools have introduced full-time pre-nursing courses which have proved of considerable value, and the Minister hopes that local authorities will stimulate interest in the courses and establish new ones where necessary. Part-time pre-nursing courses are sometimes held for girls who leave school at 15 and begin earning a living. The wastage from these courses is often high, but local authorities are asked to provide them where needed. The wastage may be reduced if the girls obtain advice from the youth employment officer.

POSTGRADUATE LECTURES IN PARIS

A three-day series of lectures for postgraduate students was held at the Hôpital Broussais, in Paris, on May 19, 20, and 21. These "Journées Médicales Annuelles" have been a regular feature at this hospital since the end of the war. About 150 doctors from a number of different countries attended.

At the opening session Professor LÉON BINET, Dean of the Paris Faculty of Medicine, discussed the gap which separates clinical from biological death. During this phase resuscitation was often successful if suitable conditions could be obtained. Professor SANTY mentioned the great strides made recently in the surgery of bronchial carcinoma, recalling the various types, their differential diagnosis, and the special difficulties of bronchoscopy.

Professor KOURILSKY stressed the frequency of certain infectious states related to upper respiratory or dental infections. Dr. ISRAEL defined a number of syndromes which result in transitory shadows in the lungs. Where these radiological changes were associated with eosinophilia (Loeffler's syndrome), they might be due to asthma, parasites such as ascaris or flukes, or certain drugs; with leucocytosis and mononucleosis they might be due to whooping-cough, lymphocytic choriomeningitis, and in a few cases primary atypical pneumonia; whereas without special blood changes such radiological findings might be attributed to tuberculosis, virus pneumonia, Q fever, influenza, psittacosis, or in most cases primary atypical pneumonia.

Professor HAMBURGER spoke on the treatment of acute tubular nephritis of toxic origin and showed how a better understanding of the aetiological factors had resulted in more scientific treatment. Professor LENÈGRE reviewed the treatment of oedema in cases of mitral stenosis, and Dr. FRILEUX discussed phlebitis.

Professor RENÉ LERICHE gave a lecture on the surgery of arteritis of the lower limbs. Dr. LORTAT-JACOB described four cases of "diffuse nodular myomatosis" of the oesophagus. The condition was distinct from muscular hyperplasia; careful palpation of the oesophagus at operation revealed the nodularity; histological study showed muscular fibres of different sizes, often grouped in whorls, suggesting myoma, or myomatosis, according to the extent of the change. The radiological appearances varied, but often a succession of spasms at different levels was shown.

Professor BERNARD reviewed the experimental data on vitamin B_{12} and suggested that it might have a direct action on the alimentary and nervous systems, over and above the indirect effect on these systems of improved haematopoiesis. Dr. LICHTWITZ, considering new trends in endocrinology, stressed the triple action of hormones, on glands, on metabolism, and on selected tissues. Professor JAYLE described recent work on the follicular hormone.

Other lectures which proved of interest were those by Professor FAUVERT on needle biopsy of the liver; Professor DOMART on the histological examination of smears from bronchial secretions, vaginal secretions, and skin lesions; Professor DE GENNES on A.C.T.H. and cortisone; Professor PASTEUR VALLERY-RADOT on migraine; Dr. HALPERN on allergic oedema; Dr. TZANCK on cross-sensitization; and Dr. LAPORTE on the recent applications of "aureomycin" and "chloromycetin." Lectures were also given on the hormonal treatment of certain disturbances of pregnancy; obstetrical analgesia; advances in electroencephalography; the differential diagnosis of septicaemic states; and on recent developments in the chemotherapy of cancer.

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE

REPORT FOR 1948–9

The London School of Hygiene and Tropical Medicine, with the appointment of its first full-time dean, Dr. Andrew Topping, has lately entered upon its second period of post-war reconstruction. Professor J. M. Mackintosh, who held the office of dean for over five years, is now devoting the whole of his time to the chair of public health. A report on the work of the School for the year 1948–9 has just been published. The teaching for the three diplomas was in full swing during that year, though some long-awaited developments in research were still hampered by lack of accommodation. In the department of entomology good progress was made in the preparation of an entomological museum. Many visits overseas were paid by members of the staff. Two visited Malaya and Ceylon on a grant from the funds of the School. Another was seconded to the Rockefeller Foundation to act as consulting entomologist in the mosquito-eradication campaign in Sardinia. Reference was made in the previous report to the discoveries in the department of parasitology relating to the life cycle of malarial parasites. At the end of the year a team under the leadership of Professor H. E. Shortt succeeded in elucidating the pre-erythrocytic cycle of the parasite which causes malignant tertian malaria.

In the department of public health Professor Mackintosh says that it is evident that the number of students who follow up the postgraduate courses for the D.P.H. at the School by entering the public health services of local authorities in this country is on the decline. It is, of course, gratifying that the course for the diploma is broad enough to attract students for its own sake, but this "only serves to throw darker shadows on the factors that are rendering a career in public health in this country unattractive to students at the present time." No doubt a remedy will be found, but in the meantime many promising public health students are being diverted from a chosen career as medical officers of health.

For their elective studies this year the students for the diploma were offered a choice of special courses in industrial hygiene, hospital administration, and tropical hygiene. The most sought after was the industrial hygiene course, for this has the further advantage of carrying the students well on the way to qualifying for the examination for the D.I.H. The aim of the elective course, however, is not to provide training for consultants in industrial medicine, but to make "good general practitioners in industrial health," whether whole- or part-time.

Separate reports are given of the work in the medical statistics, applied physiology, and other departments, and also in the Ross Institute of Tropical Hygiene. In the India and Pakistan branch of the Institute inquiries have been started into the activity of D.D.T. and of "gammexane" against the common carriers of malaria in Assam and against the sandfly vector of kala-azar, which is an extremely important disease in some parts of that country. There is preliminary evidence to suggest that D.D.T. may have some disadvantageous irritant activity which partially neutralizes its effects, and this subject is being pursued in a special investigation.

A special tribute is paid in the report to the late Professor Major Greenwood, whose death has cast a shadow over the School. "For the advancement of learning and truth, of toleration and honesty of purpose, of the ideals of this School, which he loved so dearly, Professor Greenwood was always and without stint 'as serviceable as possible' (words of his own which he laid down as the aim of his colleagues and himself). It is, with an understatement characteristic of him, in truth, no mean epitaph."

TRAINING COLLEGE FOR MIDWIFE TEACHERS

OPENING CEREMONY

Professor Hilda Lloyd, President of the Royal College of Obstetricians and Gynaecologists, formally opened on June 15 the Midwife Teachers Training College, at High Coombe, Kingston Hill, Surrey. This national residential college was set up as a result of the comments on midwife teachers' courses made in para. 173 of the Report of the Working Party on Midwives. Sixteen students, selected by examination and interview, will be accommodated at High Coombe for a six-months course, the first of which is already being run. Their theoretical studies are to be linked with practical work at Kingston Hospital and the Nelson Hospital, Merton. Two years ago, as an experiment, two intensive residential courses

of four months each, but confined to theoretical instruction, were conducted by the Royal College of Midwives, but the Central Midwives Board felt that to be of value residential instruction for the diploma should be of somewhat longer duration and should be related to practical midwifery and practical teaching, and the new venture has been designed to meet this need.

The College is run by a council composed of representatives of the Royal College of Midwives, the Central Midwives Board, the Royal College of Obstetricians and Gynaecologists, the South-west Metropolitan Regional Hospital Board, the Ministry of Health, and the University of London. The students will pay £60 for their board and lodging, and also a fee to cover the cost of tuition; students employed within the National Health Service may be seconded to the course on full pay.

At the opening proceedings Mrs. Mary Stocks, who was chairman of the Working Party and is chairman of the council of the new College, expressed the hope that individuals and organizations would make gifts to this venture, and she mentioned a gift from the Rathbone Trust and another, for the teaching of analgesia, from the National Birthday Trust. Mr. Arnold Walker, chairman of the Central Midwives Board, in welcoming the establishment of the College, paid a tribute to those who had been responsible for earlier ventures in providing residential courses for midwife teachers on a more limited scale. Miss M. Liddiard, president of the Royal College of Midwives, recalled the pioneer work of her College in the instruction of midwife teachers, and spoke of the great improvement which the new College represented as compared with the old method of part-time instruction. For many years instruction for the midwife teacher's diploma has been almost entirely on a part-time basis, and this has imposed a great strain on the midwives. Miss Liddiard emphasized, however, that in the better education of the midwife the paramount claims of the mother and baby must never be forgotten.

In declaring the College open, Professor Hilda Lloyd, one of the first women to be appointed to a chair of obstetrics and gynaecology (at her old university, Birmingham), said that the Royal College of Obstetricians and Gynaecologists, of which she was president, had the welfare of all midwives very much at heart. The midwife was the backbone of the obstetric service, and the Royal College had always appreciated the great extent to which the doctor relied on the midwife. It had been suggested that the National Health Service was encroaching on that position. She felt that they must be careful to preserve the midwife–doctor relationship. The midwives had to work as colleagues with general practitioners, but there was no doubt that the bulk of normal midwifery was in the hands of the midwife—and long might it remain so. Not only in the domiciliary service but also in the hospital the midwife was important, and it was vital that the teachers of midwives should be well trained.

The principal of the Midwife Teachers Training College is Miss L. E. Beulah, and the senior lecturer Mr. J. V. O'Sullivan, F.R.C.S., F.R.C.O.G.

Reports of Societies

THE RHEUMATIC STATE

The presidential address in the Section of Epidemiology and State Medicine of the Royal Society of Medicine was delivered on May 19 by Dr. W. H. BRADLEY, whose subject was "The Mechanism and Prevention of the Rheumatic State." Sir ALLEN DALEY was in the chair.

Dr. BRADLEY asked the meeting to consider as separate problems a "factor of infection" and a "genetic factor." He spoke first of the family incidence of rheumatism, illustrated from his own researches and from the work of Pickles and others. To enlarge his experience with regard to the factor of infection, some years ago he went to New York, where for nine months he was able to follow patients with a history of acute rheumatism into their own homes in order to observe the spread of *Str. pyogenes* in their families. He described the results. Sometimes the first attack of rheumatism after sore throat was sufficiently predictable to make it worth while to study antibody response and blood changes right through the attack, commencing with the precursor sore throat. The pattern of antibody response (as measured by the antistreptolysin "O" titre) was constant and no less characteristic than in any other communicable disease. There was a good deal of scarlet fever in New York at that time, and he was satisfied that, for practical purposes concerning the mechanism of the rheumatic state, scarlet fever and streptococcal sore throat were manifestations of one disease precipitating the rheumatic state.

He was struck particularly by the occurrence of pallor coincident with the rise in the blood sedimentation rate when an attack of acute rheumatism was to be expected. Pallor was an obvious feature in those cases which developed the common picture of acute rheumatism. On his return to this country he joined the late Dr. John Ryle at Cambridge and continued his studies. He found that the rise in the blood sedimentation rate which heralded the rheumatic attack and persisted during its course was intimately related to the fall in packed cell volume and to the pallor, and he came to the conclusion that the anaemia was a dilution phenomenon largely independent of red-cell destruction. He then carried out some blood-volume estimations which confirmed this finding. Dr. Bradley gave a careful description of his studies and conclusions. Given the circulating plasma volume and the plasma protein per unit volume, it was possible to compute the amount of the circulating protein, and from such calculations he found that sometimes more than twice the normal circulating globulin was present during the early stages of acute rheumatism. The increase in total protein was of course associated with an increase in specific gravity and in serum volume. The results were surprisingly consistent in a number of cases. The total circulating proteins had their highest levels during the height of rheumatic activity and fell as the condition became quiescent. He showed these protein changes as demonstrated by electrophoresis and high speed centrifuge studies.

Mechanism of Rheumatism

If rheumatism was an infective condition and the globulinaemia the expression of an antibody response to a specific infection, antibody production would be expected to rise during the illness and to persist after recovery, but this was not the case. The rise occurred at the onset of rheumatism in those cases in which he was fortunate enough to watch the disease from the beginning of the acute streptococcal infection. His conclusion was that the high globulin level was not merely an effect but might play a causal role in producing the abnormalities we call rheumatism. When acute *Str. pyogenes* infection occurred it was followed by a lag period, and by the time the rheumatic process was active this infection was no more than a remote cause, and a new mechanism almost certainly involving an inherited factor had come into operation as a continuing cause of the rheumatic state.

During the war one of his tasks at the Ministry of Health concerned hepatitis. He had already described to the Section the work done on the transmission of this disease to patients with rheumatoid arthritis. In some patients in whom jaundice was induced the relief of rheumatism was very convincing and appeared to be related to the suspension of liver function and not the jaundice. Hench had said that the effect of cortisone closely resembled the effect of hepatitis in rheumatoid arthritis. Dr. Bradley guessed that the most important physiological function of cortisone in the relief of rheumatism was the conversion of protein to glycogen. The hypothesis that, in the cure of the rheumatic state, cortisone worked through its function as an "S" hormone, effecting the conversion of protein into glycogen, deserved more attention.

From the inception of their work in this field the Mayo Clinic investigators had emphasized that cortisone must for the time being be regarded as a research tool rather than as a practical therapy. He felt strongly that epidemiologists must

not allow the factor of infection to be forgotten, and that the hope of evolving a practical therapy must not be made a reason for delaying a definite attack upon the prevention of the rheumatic state.

Prevention of Acute Rheumatism

The remarkable decline in the incidence of streptococcal disease in recent years, which had begun before the discovery of antibiotics and chemotherapeutic agents, might not continue indefinitely. The decline in acute rheumatism obviously had nothing to do with the inheritance factor; it was inconceivable that it should have resulted from a process of natural selection in the course of a couple of generations. All the data assembled pointed to the fact that infection had ceased to operate so vigorously. An upward swing in the curve of scarlet fever would be the first hint of the beginning of a new cycle of streptococcal disease and of acute rheumatism. The epidemiologist knew that unexplained trends in the incidence of communicable disease had a way of reproducing themselves, and it might be possible to steal a march on the streptococcus and influence the incidence of rheumatic heart disease, already on the increase in some districts.

In the prevention of acute rheumatism there were four key points: (1) A considerable proportion of genetically predisposed persons could be detected on the basis of family history. (2) Chemotherapy, although valueless in the treatment of the rheumatic state, had been applied successfully to the prevention of relapse of rheumatism. (3) It was not impracticable to protect genetically predisposed individuals from contact with *Str. pyogenes*. (4) The restriction of the size of rheumatic families would increase the possibility of the survival of the members and reduce the production of rheumatic stock.

Broadly speaking, the children of rheumatic parents should be brought under surveillance, housed in single bedrooms, employed in the fresh air away from the big towns, nourished adequately, adapted to chemotherapy, and encouraged to protect themselves from upper respiratory tract infections. They should be advised never to marry a rheumatic subject, and to restrict their families so as to provide each child with a protective environment.

Recapitulating, Dr. Bradley said that given a factor of inheritance (involving Mendelian characters), and a factor of infection, they could speculate with some degree of assurance that the mechanism of the rheumatic state depended upon an abnormal response to a specific antigen. The inherited factor was not communicable, but the factor of infection appeared to be *Str. pyogenes*, a very common communicable agent capable of control.

With less assurance it could be postulated that the genetic abnormality resided in the physical characters of the antibody produced by "rheumatic" persons or in the disposal of antibody by such persons. At the beginning of the rheumatic attack—not during the precursor fever—there was an increase in blood volume and in the specific gravity of the serum. From the beginning of the attack antibody protein had been mobilized as if in response to a previous stimulus. These changes were associated with a great excess of globulin and a resultant increase in plasma volume. If one regarded the pallor and cardiac dilatation and the "effusions" of a case of acute rheumatism in the light of this "hydraemia" one saw a very simple mechanical explanation of some rather striking signs. The histology of the fulminating case of rheumatic fever fitted the same explanation.

Perhaps cortisone worked by virtue of the conversion of protein into glycogen, and he was rather encouraged to make that suggestion by the dramatic effect which occurred when hepatitis upset the protein metabolism in a person suffering from rheumatoid arthritis.

Be this as it may, there was already much that could be done towards the prevention of the rheumatic state, and Dr. Bradley concluded by quoting from Sir John Parkinson's Harveian oration: "Let us persist in a spirit of post-war dedication and work in hope and confidence for the ultimate defeat of this the most deadly enemy of youth."

Correspondence

Colour-vision

SIR,—May I make three comments on the leading article on colour-vision (June 10, p. 1355)?

(1) The author of the article refers to Professor Motokawa's method as a "blunderbuss mode of stimulation." Actually the stimulus used is one of a fraction of a milliamp obtained from a twelve-volt battery via a resistance of 10,000 ohms; a current insufficient to light even the smallest electric light. This tiny current is passed through part of the observer's head for one-tenth of a second, one electrode being above the brow and the other on the temple of the eye to receive stimulation. The part of the current actually reaching and stimulating the eye must be smaller still. Anything less like a blunderbuss would be difficult to imagine. A "micro-micro-blunderbuss" might perhaps express it.

(2) The author suggests "that until more is known about what such a blunderbuss mode of stimulation actually does the significance of these results must remain in doubt." I regret I cannot agree. We do not know what an electric current does either to a nerve or to a muscle when it is used for purposes of stimulation. But that does not stop us from using this method of stimulation and in fact it is widely used. Here is an analogous point: we do not know exactly how living tissues generate electric currents. If then it were true that the significance of an electrocardiograph or an electroencephalograph must remain in doubt, because we do not know how the currents originate, then these valuable methods of diagnosis, together with several others, would not be available to us. In Professor Motokawa's case the matter appears to me to be as follows: When the light stimulus is turned off a supranormal phase of enhanced sensitivity follows. That is, enhanced sensitivity either to light itself or to an electric current which is causing a sensation of light. This supranormal phase of the eye closely resembles, if it is not identical with, the supranormal phase which occurs in a frog's sciatic nerve during the period which immediately follows electrical stimulation. It also closely resembles the supranormal phase found in the auditory nerve of the cat. Thus the supranormal phase is already known to us and Professor Motokawa is not breaking new ground when he investigates it. The newness of his method depends on his use of the supranormal phase as a means of investigating the properties of the receptors. There is no doubt that this new method is in its early stages, and that there are several other visual states to which it can usefully be applied. But I do not agree that the results so far produced are in doubt merely because we do not know precisely how the supranormal phase arises.

(3) The author of the article writes: "The phenomena of colour mixing can be described in terms of three variables, and this finding has been amply substantiated by the sound experimental work of Wright, Stiles, and many others." Now this statement as it stands is true, but the implication that this is in accordance with the Young–Helmholtz theory is quite false, for the following reasons: "a variable" may be either positive or negative, but "a given sensation" can be of only one kind, it is either there or it is absent; it cannot be negative. The same statement applies to a stimulus, and there is no such thing as a negative stimulus. In consequence, the statement that any given spectral colour can be described in terms of three variables is true, but the statement that any given spectral colour can be matched by means of three spectral stimuli is false. An example may make this distinction clearer. Spectral yellow can be described in terms of three variables, red, green, and blue. The red and green variables have positive values, but the blue has a negative one because the equation for yellow (of 0.58 μ wavelength) is: $Y = 0.604\ R + 0.414\ G - 0.018\ B$ (see p. 135 of *Researches on Normal and Abnormal Colour Vision*, by W. D. Wright). The reason for the negative value of the blue coefficient is that the amount of blue which this coefficient represents has to be mixed with the spectral yellow in order to desaturate

it. If this is not done the spectral yellow is always more saturated than the red-green mixture, which otherwise superficially matches it. Thus the statement that yellow can be described in terms of three variables is found to be true.

Let us similarly examine the statement that yellow can be matched by means of three spectral stimuli. Experiments done years ago showed that yellow spectral light could be matched very nearly by a mixture of spectral red and spectral green lights. It seemed likely at that time that the failure to match exactly might be due to optical imperfections in the spectroscopic apparatus which was used to produce the spectral colours. Thus with improved apparatus, producing more saturated spectral colours, a more perfect or even an exact match might be expected. But in fact the exact opposite has been found, because using modern apparatus, such as Wright's trichromatic colorimeter, which gives spectral colours of very high saturation, the difference between pure spectral yellow and the red-green mixture is even more marked to-day than it was years ago. Moreover, if we add blue to the mixture we make matters worse, and not better. Thus it is not true that spectral yellow, or any other spectral colour for that matter, can be matched by mixtures of three spectral stimuli. Now this is a setback to the three-colour theory of the most fundamental importance. It strikes straight at its foundations, and is one of the reasons for the adoption of the polychromatic theory.—I am, etc.,

London, W.C.1. H. HARTRIDGE.

Management of the Menopause

SIR,—A friend on the B.B.C. tells me that some elementary talks given on the "Change of Life" were followed by hundreds of letters, mostly from menopausal women complaining of symptoms and asking for advice. The gist of these letters appears to be that the family doctor did not consider the symptoms serious enough to treat, or for various reasons no help had been forthcoming. Most of the complaints came from women who were suffering from flushes, insomnia, or anxiety, or who felt the exaggerated depression and irritability so common to premenstrual women. My own experience of such women is that if they are not treated they become a source of misery to themselves and to others, and may become seriously embittered. Yet patients sometimes express the belief that doctors will not trouble to treat menopausal complaints.

It seems to be true that many practitioners do not offer endocrine treatment at all, nor, perhaps, really appreciate the amount of morbidity which their refusal entails. The subjective symptoms of a menopausal woman can be totally disabling, and if valerian, etc., fails to help, withholding oestrogen would seem no more justifiable than withholding insulin from a diabetic. The fact that the phase will pass within months or years surely should be no contraindication to giving help. Confusions arose in the past because of failure to standardize the early oestrogens and to recognize that the menopausal woman should have far smaller doses than those usually prescribed. I have been taught a technique which seldom fails, provided certain rules are observed.

1. That the standard unit for treatment should be 0.1 mg. of stilboestrol (Boots, B.D.H.), or the equivalent. If the patient proves to be intolerant of the drug—and about one in seven experience nausea—pure oestrone (Organon) in 0.1 mg. tablet is almost always tolerated. Unfortunately it is expensive. I have not myself been impressed with ethinyl oestradiol, but have colleagues who use it with success.

2. If the patient has flushes to guide her, she may be allowed to start with one tablet daily, adding an extra one each day until the flushes are controlled. This dose will generally range from two to eight tablets daily. By that time she usually "feels herself" again. Dosage kept on the lower side of this can be considered her immediate optimum. It can be reduced or discarded, often after a very few weeks.

3. If the patient is still menstruating she can treat herself thus for the first three weeks of a cycle. If menses have ceased she should omit treatment for one week out of every four. She should be instructed to keep her dose to the lowest compatible with well-being, and to report herself without fail in, say, six to twelve weeks.

4. Where menorrhagia, uncontrollable by calcium, is present a different approach may be desirable.

Many menopausal women are better treated by thyroid than by oestrogen. The exhausted, depressed patient whose concentration fails may be one who requires this therapy. She need not, as Dr. Asher reminded us in his article "Myxoedematous Madness" (September 10, 1949, p. 555) exhibit all the classical signs of thyroid deficiency. Most subjective menopausal symptoms yield to one or other or both of these lines of approach. Menorrhagia may present therapeutic problems of its own, but it is often caused by subclinical myxoedema, when it yields to thyroid, gr. 1 or 2 daily (65 mg. or 0.13 g.). Few other patients appear to get so little professional consideration as some of these menopausal women, and yet their symptoms can be easy and gratifying to treat.—I am, etc.,

London, N.W.1. JOAN MALLESON.

Immunization and Poliomyelitis

SIR,—I would very much like, as one who is a mother and not a doctor, to give my views on the controversy about immunization. It may possibly aid the medical profession in presenting facts to the public.

Dr. Mary E. Budding (May 27, p. 1273) suggests that it is mothers of lower intelligence who refuse to have babies immunized. That is not necessarily so, for intelligent parents look much further ahead, and what they see can be positively alarming. It seems quite clear from various reports that a foreign infection is not actually introduced by the immunization, but that the immunized child with a temporarily lowered resistance is easily susceptible to germs which he may otherwise resist, such as poliomyelitis. The problem facing a mother is this: should she have her child immunized and thus expose it to a crippling disease which may affect the whole of its life, or should she forgo the immunization and console herself with the fact that the child will probably never contract diphtheria and that if it does there is little chance of it being fatal because of the great advances in its treatment? This problem is a heart-breaking one, and the responsibility of making a decision is very worrying.

My next point is about the results of pertussis inoculation. As it has been proved that in rare cases cerebral troubles have been the result, and although a mother can appreciate the word "rare," yet she inevitably wonders if perhaps her child will be in this category. Again, she probably also wonders how many cases of slight backwardness, which never come forward as medical cases, may be due to the effects of immunization, and there is in fact an increase in the number of backward children. So the instant reaction is to place that fact side by side with the increase in immunizations. Here, also, as with diphtheria, there is slight consolation that if the child does get whooping-cough the treatment now is much more skilled.

Mothers are not just accepting rumours and stubbornly refusing immunization. They realize that they face a grave problem and would like to know the scientific facts for and against, that they may be helped to make a decision. I had my first two babies both vaccinated and immunized. Now I dare not have the third one done until I know more, and the situation is a very uncomfortable one.—I am, etc.,

Sunderland. MARGUERITE DARNTON.

Double Primary Carcinoma

SIR,—A rough check of the University College Hospital Follow-up Department's records shows that 18 cases of double primary carcinoma have been registered since January 1, 1946. This is 0.72% of all registrations. Dr. M. Lethbridge Farmer (April 15, p. 905) will be interested to learn that five of these were bilateral breast carcinomata, but it is, of course, difficult to exclude the possibility of metastasis in such cases.

In six, one of the growths was a rodent ulcer; the second primary growths were, respectively, gastro-intestinal carcinoma (two cases), epithelioma of the skin (two cases), carcinoma of alveolus and rodent ulcer (one case each). One case of intrinsic carcinoma of the larynx developed an epithelioma of the skin two years later, and one case of carcinoma of the vallecula

developed a carcinoma of the anterior faucial pillar shortly after finishing a course of deep *x*-rays to the first primary growth. One case was of multiple carcinomata of the colon associated with polyposis, and another, presenting with an epithelioma of the anus, was also found to have a carcinoma of the rectum. Two cases presenting with symptoms referable to carcinoma of the ovary (subsequently proved by operation and section) were also found to have carcinoma of the breast. One case, at the moment under *x*-ray treatment for local recurrence of carcinoma of the ovary, has a lump in one breast which has all the physical signs of carcinoma.—I am, etc.,

PETER DELLER,
Cancer Registrar.

London, W.C.1.

Vascular Changes in Diabetes

SIR,—Dr. Elliott P. Joslin (May 13, p. 1095) stresses the change in the hazards his diabetic patients have to face in the present era, when, as a result of insulin therapy, their duration of life has trebled.

Diabetic coma, formerly responsible for two-thirds of the deaths, only claimed 1.9% of victims among Dr. Joslin's 2,299 diabetic patients who died between 1944 and 1949. Deaths from tuberculosis and other infections have fallen to less than half the previous figures. On the other hand, the mortality from cardiovascular-renal diseases has reached the high figure of 70.1%, exceeding that from diabetic coma in pre-insulin days. Among Dr. Joslin's large number of child diabetics 54.5% of deaths were from this cause. What is even more distressing is the high incidence of retinopathy among diabetics who have had the disease for some years.

The association of diabetes with vascular damage in various organs was described as a pathological entity and termed "intercapillary glomerulosclerosis" by Kimmelstiel and Wilson[1] in 1936. Subsequent workers[2,3,4] have recognized that this is a terminal phenomenon in the clinical triad of hypertension, retinopathy, and albuminuria. According to Wagener,[5] the earliest and basic lesion is the small punctate retinal haemorrhage in the presence of apparently normal retinal vessels as seen by the ophthalmoscope. These retinal haemorrhages may absorb spontaneously and escape notice because of lack of appreciable interference with vision. On the other hand, they may progress to blindness, when retinitis proliferans develops with subsequent detachment of the retina or glaucoma of the haemorrhagic type from massive vitreous haemorrhage.

In his book[6] Dr. Joslin states, "Among young patients with diabetes of more than ten years' duration retinitis proliferans presents an increasingly serious problem and deserves primary consideration. . . . Up to December, 1945, this condition was recognized in 110 patients involving 194 eyes." Albuminuria was present in two-thirds of the cases and in some of them had even preceded the onset of retinitis proliferans. Hypertension was also present in a large proportion of the patients.

In his paper Dr. Joslin (p. 1097) emphasizes that the cardiovascular-renal diseases are now the chief enemy of the young diabetic, and he goes on to say, "These young patients must in some way or other be told that if they do not keep their diabetes controlled they are liable to serious complications in their eyes, their kidneys, their hearts, or their brains. We can always offset this serious advice by emphasizing that those who are perfect after 25 years are in general those who have followed treatment the best." But is this the whole story? Dolger[7] holds that control of the blood-sugar level and of glycosuria must not be interpreted as control of the disease. He describes an analysis of the case histories of 200 patients whose diabetes began before the age of 50, including 55 juvenile diabetics whose diabetes commenced before the age of 20 (11 months to 19 years). These patients, who came from the metabolism clinic of the Mount Sinai Hospital and from private practice, were specially selected because records were available dating back to the onset of their diabetes. At each visit to the physician "month after month and year after year" a careful check-up was made with special attention to ophthalmoscopic examinations, blood pressure estimations, and urine analysis.

Among the 55 juvenile diabetics 20 satisfied all criteria for excellent diabetic control. Yet within a range of six to twenty-two years, with an average duration of thirteen years, retinal haemorrhages were noted in all. In 50% of the patients hypertension was present, and albuminuria in 30%. Of those patients in whom the diabetic control was "fair" 18 showed retinal haemorrhages within five to twenty years with an average duration of diabetes of 10.4 years. Hypertension and albuminuria were present in one-third of the cases.

The remaining 17 patients had such a "brittle form of diabetes" that willy-nilly a "free diet" was permitted. The incidence of retinal haemorrhage was noted between five to nineteen years after the onset of diabetes with an average duration of 12.4 years. Hypertension was present in 40% and albuminuria in 64%. Of these 55 juvenile patients 5 became blind.

From my own very limited experience I should like to cite the case of a man known to me personally but not a patient of mine. He developed diabetes mellitus in 1909 when he was 29 years old. From existing photographs it appears certain he would not have survived had insulin not become available when it did. Although highly intelligent and co-operative and anxious to adhere to a strict regime, he has been encouraged by his physician to "spill" because of his tendency to severe hypoglycaemic reactions. For years he has had glycosuria during some part of the day and a higher blood-sugar level than orthodox treatment would permit. Yet to-day, forty-one years after the onset of diabetes, when he has attained the psalmist's span of three-score years and ten, he is very fit, vigorous, and active, physically and mentally. His son, a medical man, assures me that his eyesight is excellent and that his physician is satisfied that he has no retinal changes, hypertension, or albuminuria. While this case supports Dolger's contention that deviation from rigid control of glycosuria and hyperglycaemia is not catastrophic it also shows that there are exceptions to Mirsky's[8] dictum: If the diabetic lives long enough he will develop vascular disease in one form or another no matter how he is treated.

Of the remaining 200 patients, the subject of Dolger's study, within a period of 25 years not one escaped retinal haemorrhage, irrespective of age of onset, severity of the disease, or type of treatment followed; 22 patients became totally or partially blind and 50% showed hypertension and albuminuria. One cannot, therefore, but incline to the view expressed by Dolger and others that carbohydrate disturbance is but one facet of the disease termed "diabetes mellitus"; that vascular damage is not a complication that can be warded off by rigid control of the hyperglycaemia and glycosuria, but that it is an associated concomitant of the disease.—I am, etc.,

CECILIA SHISKIN.

London, E.2.

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Ascorbic Acid in Rheumatoid Arthritis

SIR,—The discovery by Hench *et al.* of the dramatic improvement in rheumatoid arthritis and allied conditions by cortisone and A.C.T.H. has stimulated extensive research in this field all over the world. As mentioned in the *Journal* of April 29 (p. 1020), D.O.C.A. and ascorbic acid were tried in rheumatoid arthritis in view of a supposed abnormality in steroid metabolism. Ascorbic acid is said to be in some way physiologically active in the synthesis of adrenal cortical hormones. Reports about this method of treatment from many reliable sources revealed wide divergence of results and opinions.

Since the isolation of vitamin C in 1928, and since its synthesis in 1934, a number of papers stressed the reduced ascorbic acid content of the blood plasma in rheumatoid arthritis. From the historical point of view the most interesting contribution to the discussion on ascorbic acid in rheumatoid arthritis was by Dr. Owen Rees, of Guy's Hospital, a hundred years ago. In the *London Medical Gazette* of January 26, 1849, he reported a case of "Rheumatic Gout" treated by lemon-juice. The clinical pattern of the case is typical of acute rheumatoid arthritis.

Dr. Rees remarked that it is principally owing to the very surprising effects which he has observed from the use of lemon-juice—he could not know that 100 g. of lemon contains 50 mg. of ascorbic acid—in the treatment of rheumatic gout that he has been induced to notice this case. He has been in the habit of prescribing this remedy, with marked and rapid benefit. The early relief from pain was such that had anyone unacquainted with the remedy in use watched the progress of the case he would almost inevitably have concluded that sedatives had been employed. Among the out-patients at Guy's Hospital he has met with "several prominent examples of cure" by this method.

In his *Manual of the Practice of Medicine*, London, 1856, Dr. G. H. Barlow, physician to Guy's Hospital, mentions "one of the most ingenious methods" of treating rheumatic inflammation, and says: "Dr. Rees recommended lemon-juice to be given in doses, which he ultimately increased to two or three ounces, three or four times a day; and in a considerable number of cases the patient has become convalescent in five or six days."

The history of medicine is often a tale of discoveries that were soon forgotten, only to be rediscovered years or even centuries later and hailed as new observations.—I am, etc.,

London, E.17. B. JUHN.

A Twice-ruptured Uterus

SIR,—This case is reported because it is not often, even in Malaya, that one is called upon to treat the same patient on two occasions for rupture of the uterus.

The patient was a Chinese Hokkien, aged 28 years, of very small stature—height 4 ft. 9 in. (144 cm.), usual weight 5 st. 4 lb. (33 kg.). Her pelvis was of the justo minor type, the interspinous diameter being 8½ in. (21.6 cm.), the intercristal 9½ in. (24 cm.), and the external conjugate 6½ in. (16.5 cm.).

I first saw her on May 29, 1947, when she was carried in from a taxi in a desperate condition, with a barely perceptible pulse, groaning with continuous pain. The uterus was in a state of spasm, and there was considerable bleeding from an extensive laceration of the vagina, from which a foetal foot, a hand, and a loop of bruised cord were protruding. No foetal heart could be heard.

The story was that this was the third pregnancy, the two earlier ones having ended seven years and four years ago respectively in destructive operations after some days in labour. On each occasion she had been told that vaginal delivery was not possible for her, and that her next labour must be conducted in hospital by caesarean section. The present labour had begun two days before with rupture of the membranes and slight and irregular pains. For the past 18 hours, however, she had had strong and frequent pains, and the old lady who lived next door had examined her repeatedly, and had made many attempts to deliver her. Finally the old lady had given it up, and so the husband had summoned a taxi and driven five miles along the main road to the hospital.

Intravenous morphine and saline, followed by pentothal to relieve the pain, effected some improvement in her condition, and she was then examined under open ether anaesthesia. There was an extensive tear of the perineum, extending through the left vaginal wall to the vault and through the left side of the cervix. The laceration involved the left broad ligament. The foetus was delivered by evisceration and perforation of the head, and was followed by the already separated placenta. Investigation then showed that the tear of the broad ligament was incomplete and did not involve the peritoneal cavity. It was plugged with flavine gauze.

The convalescence was extremely hectic and complicated by considerable abdominal distension for the first week, but thanks to chemotherapy the patient survived, and her temperature gradually settled over a period of three weeks. She refused to be sterilized and left hospital against advice as soon as she was able to walk a few steps. She was warned that another pregnancy would involve considerable risk and that her only hope of surviving it would be a caesarean section in hospital before term.

I next saw her on September 9, 1949, when she walked into the labour ward, saying she had lost her card but had been in hospital before. She was luckily recognized, and her record was found at once. She had been in labour for eight hours and had had strong pains and some bleeding per vaginam for the last two to three hours. The fundus was at term. The foetal head was not engaged, but riding high above the inlet, and a foetal heart could be heard. She was rushed to the theatre, but the membranes ruptured *en route* and the head failed to engage.

The abdomen was opened under gas-oxygen–ether anaesthesia, and free blood and liquor were encountered. A living male child weighing 6 lb. (2.7 kg.) was delivered by classical caesarean section. Haemostatic sutures were inserted into the uterus and the pelvis inspected. There was a complete tear of the left lower uterine segment through the left broad ligament, which was ploughed up and greatly distorted by blood clot. On the right there was a smaller, incomplete tear involving the broad ligament. Subtotal hysterectomy was performed; haemostasis was secured with considerable difficulty owing to the distortions of the structure from old adhesions and fresh bleeding. The cervix and vagina were involved in the recent tear. She was given a transfusion a few hours later, when compatible relatives were found. Her convalescence was surprisingly smooth, probably owing to the exclusion this time of the unwashed hands of the old lady who lived next door.

She left hospital on October 2 in good condition with a healthy son. When asked why she had so persistently disregarded all medical advice she replied that she was willing and anxious to do what we had advised, but that the final decision rested, of course, with her mother-in-law, who said that babies should be born at home.

I am indebted to the Principal Medical Officer, Johore, for permission to publish this report.

—I am, etc.,

Johore Bahru, Malaya. MARJORIE J. LYON.

Brachial Neuralgia

SIR,—Dr. M. G. Good (May 27, p. 1272) states:

"For years I have been emphasizing that the majority of cases of sciatica are muscular in origin—'muscular sciatica'—caused by a polymyalgia of hip muscles (quadratus lumborum, glutei, tensor fasciae latae), and can be cured by procaine injection of the appropriate myalgic spots without ever resorting to the ordeal of a laminectomy."

I suggest that Dr. Good watches some operations for prolapsed intervertebral disk carried out by reputable neurosurgeons or orthopaedic surgeons. When he sees how the "root" of the matter is dealt with he may desist from attempting to score "outers" with his needle.—I am, etc.,

Norwich. H. A. BRITTAIN.

A Simple Method of Bronchography

SIR,—Drs. D. E. Vaughan Jones and M. R. William Spacek have recently described a technique for the instillation of iodized oil into the trachea (May 13, p. 1140). Professor R. R. Macintosh and Dr. William W. Mushin (June 3, p. 1319) subsequently pointed out that the Magill tube is unnecessary and in the case of small children may cause difficulty. We have developed a technique for rapid bronchography in the chest clinic which is essentially similar to that recommended by Professor Macintosh and Dr. Mushin in that a fine rubber catheter is employed. No originality is claimed for our method, but the details may be of interest to others seeking a safe and easy means of carrying out bronchography in adults and older children in the out-patient department.

Strong sedation has been found quite unnecessary, and indeed is best avoided so that the patient's full co-operation may not be impaired. His assistance is further ensured by a preliminary explanation of the purpose and technique of the procedure. A subcutaneous injection of atropine sulph. gr. 1/100 (0.65 mg.) and codein phosph. gr. 1/8 (8 mg.), or proportionately less in children, is given half-an-hour beforehand, together with a dose of linctus codein and a tablet of "decicain" (amethocaine) to suck. With the patient sitting comfortably facing the operator and holding his own tongue forward, the larynx is sprayed with 2% "butyn." A Jacques rubber catheter (size 9 English gauge for adults, 5 or 6 for children) is lubricated with a jelly containing 2% "butyn" and passed through the nostril so that the tip comes to lie just behind the epiglottis. If necessary its position can be checked with a laryngeal mirror. At the end of expiration "butyn," ½ to 1½ ml., according to the size of the patient, is squirted rapidly through the catheter, and when coughing has subsided the tip of the catheter is pushed on down between the vocal cords to lie in the trachea, and the upper end is secured to the forehead.

Respiration is in no wise hindered by the narrow tube, which remains in position throughout bronchography without causing discomfort. The patient can move freely and oil can be instilled through the catheter with the patient in any desired position. Satisfactory coating of all or any of the bronchi should be obtained without difficulty, and there is very little tendency for the patient to cough

or for the oil to flow back into the pharynx. Intubation usually takes less than five minutes and the operation is well tolerated, even by children.

The youngest child on whom I have used this method was a little girl of 6, and the results were most satisfactory. If the confidence of the child can be won, it may thus not be necessary to use general anaesthesia for bronchography in children over the age of 7. With such a simple and reliable method available, the continued use of so traumatic a technique as cricothyroid puncture can, I would submit, no longer be justified. It should be finally abandoned as a medical anachronism.—I am, etc.,

Southend-on-Sea. E. G. SITA-LUMSDEN.

Valvulotomy for Mitral Stenosis

SIR,—I should like to raise a query on the article by Dr. Charles Baker, Mr. R. C. Brock, and Dr. Maurice Campbell (June 3, p. 1283) on "Valvulotomy for Mitral Stenosis." In the story of Case 3 there is printed that, "During all intracardiac manipulations the left common carotid artery was compressed by the anaesthetist to lessen the chance of cerebral embolism." Is this not an oversimplification and a waste of the anaesthetist's time, for surely any retarded embolus will proceed when the compressing force is released?—I am, etc.,

Glasgow, S.2. ALBERT A. CHAZAN.

The Medical Bill

SIR,—Dr. J. Keith Carter and Mr. W. B. Manley, in letters (May 27, p. 1270) relating to the Medical Bill, 1950, expressed some concern over the effects the Bill may have, and the latter states that the Bill has passed through the House of Lords without any protests from those affected. I wish to point out that when the Bill was first introduced the British Medical Students' Association immediately considered it in detail and prepared a report which was circulated to all medical schools. Opinions were invited, and after considering reports from the various schools we have established a policy which we believe to be truly representative of medical student opinion.

While the B.M.S.A. is in general agreement with the principle of the Bill, we are concerned about its implementation and we took steps to draw the attention of medical members of the House of Lords to our opinions and recommendations. Many of these recommendations were raised in the House of Lords at the debate stage by Lord Horder, who is an honorary vice-president of our association. The B.M.S.A. intends to do everything in its power to keep the students' point of view before those concerned.

We consider that the status which is to be accorded to the provisionally registered doctor is by far the most important point at issue. We believe it to be essential that his duties and responsibilities should be the same or very similar to those at present enjoyed by housemen in teaching hospitals. In this connexion we feel that if the maximum benefit is to be obtained from these appointments then the number of patients allocated to each house-officer should never fall below a minimum of twenty. We believe that the choice of appointments available to the newly qualified doctor should be as wide and as free as possible and we are convinced that the salary, like the status, of these officers should not be less than that at present paid.

As students we are particularly concerned with the effect the Bill may produce upon undergraduate teaching. In the past the British medical student has been given great opportunities to acquire personal experience and skill in the wards. It is possible that with the introduction of a "compulsory year" this emphasis on practical work in the teaching of medical students may be sacrificed.

The "appointed day" for the implementation of the Act is not yet known, and this is a matter of concern to many students. Students who prepared for a 5½-year course may well be involved in an additional financial burden. This particularly applies to married students with families, who will also have an enforced separation for at least a year. Further, if the Act comes into force whilst a period of military training is still compulsory it will mean that at least eight years must elapse between commencing studies and entering practice. We therefore consider that the "appointed day" should be deferred until after the expected date of qualification of those who have already commenced their studies.

Having regard to the amendments already introduced into the Bill and to the discussion which took place in the House of Lords, we are preparing a further statement of the student view which will shortly be presented to medical members of the House of Commons.—I am, etc.,

P. L. C. DIGGORY,
London, W.C.1. President, British Medical Students Association.

Popular Health Journal

SIR,—In response to Dr. R. Prosper Liston's request (June 10, p. 1375), may I suggest *The Hypochondriac*? It has at least the merit of indicating the kind of reader to whom the proposed new journal is most likely to appeal.—I am, etc.,

Streatley, Berks. ROBERT HUTCHISON.

POINTS FROM LETTERS

Poliomyelitis and Immunization

Dr. E. GRANGER (Thame, Oxon) writes: Though it is still doubtful whether immunization against diphtheria and pertussis has anything to do with the incidence of poliomyelitis, and even more improbable that diphtheria is in any way antagonistic to poliomyelitis—this latter has not even been suggested—nevertheless this should be food for thought, and statistics might show that when one disease is on the increase another is waning. Poliomyelitis may now be more prevalent because some other ill, preferably something non-notifiable, is dying out. . . .

Allergic Dermatitis of the Eyelids

Dr. F. W. SIMPSON (Perth, Australia) writes: I have seen so many cases of this condition during the past six months that I have come to the conclusion that the allergen must obtain entry through the eye itself. How else can it be that only the eyelids are affected? The usual antihistamine drugs have proved quite useless, and I have found the best treatment to be adrenaline used as drops and subconjunctivally. A typical case was that of a woman aged 31 who every year for four years in the spring has suffered from intractable urticaria of the eyelids. Only recently did we trace its cause as orange blossom. Why should orange blossom upset only the eyelids unless it obtains entry through the surface of the eye itself? . . . It is well known that in cases of atropine intolerance a drop of atropine instilled in the eyes will induce gross swelling of the lids. Similarly allergic dermatitis of the lids must be caused by the excitant entering through the eye, and the treatment of the condition must be made by the same path.

Mass Vaccination

Dr. H. TUDOR EDMUNDS (Slough, Bucks) writes: Dr. A. W. Fowler (May 27, p. 1272) is to be congratulated on drawing attention to the anachronistic nature of mass vaccination in this country. . . . However, there is a more serious aspect from the public-health point of view. We have to face the cold scientific fact that, while repeated vaccination often fails to prevent smallpox, it modifies its appearance and makes it very difficult to diagnose. As a result of this the recent outbreak in Glasgow was caused by an Asian seaman who had been "thoroughly vaccinated" previously and who was examined by a number of doctors, none of whom was able to recognize his illness as smallpox. Yet this man gave the illness to a number of other people, including one doctor, who died from it. Had this seaman not been vaccinated previously his attack of smallpox would have been recognized as soon as he was examined and adequate precautions taken to protect those who attended him.

Morphine in Asthma

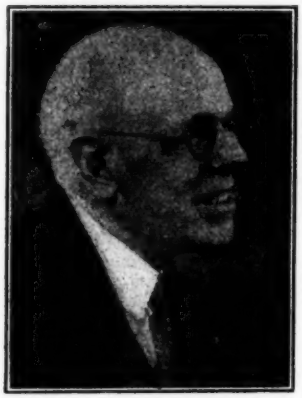
Dr. GEORGE GILLETT (Ramsgate) writes: A week ago I was called out to a very severe case of asthma. I attempted to inject "cardophyllin" intravenously but failed, owing to the distress of the patient, and so I gave him morphine gr. 1/5 (13 mg.) and atropine gr. 1/100 (0.65 mg.) subcutaneously. Four hours later I called to see him and he was drowsy, very much easier, and, his wife informed me, coughing up his sputum easily. In my opinion if morphine is given with not less than 1/100 gr. atropine in these cases it is free from the objections raised against it by contributors to this correspondence.

Obituary

W. F. SNOW, M.D.

A wide circle of friends in the U.S.A., in this country, and indeed in many other countries, will be grieved to learn that Dr. W. F. Snow dropped dead in a street of Bangor, Maine, in the afternoon of June 12. Dr. Snow, whose sudden death was reported briefly in last week's issue of the *Journal* (p. 1439), was chairman of the board of directors of the American Social Hygiene Association and president of the Union Internationale Contre le Péril Vénérien.

William Freeman Snow was born in 1874. After graduating B.A. in chemistry at Stanford University and taking later the M.A. in physiology, he proceeded M.D. in 1900. Subsequently he studied at Johns Hopkins and other institutions in the U.S.A. and abroad. He soon joined the teaching staff of Stanford University and from 1902 to 1919 was professor of preventive medicine there; from 1908 to 1914 he was also State health officer for California. In these offices he became known as a man of energy, tact, and wisdom, and in 1913 he was persuaded to undertake the direction of the newly formed American Social Hygiene Association. This organization, now a powerful one, owes its origin to such men as President Emeritus Charles W. Eliot, of Harvard, and Dr. Prince Morrow, of New York, who were then the leaders of organizations trying to promote sex hygiene, and to President David Starr Jordan, of Stanford University, who headed a movement against commercialized prostitution. These and others, seeing the need for a voluntary agency with the broadest possible approach to the problems of social hygiene, merged several existing societies together to form the A.S.H.A.



Snow became principal adviser on the prevention of venereal diseases to the American Army on its entry into the war of 1914–18, and on this part of his work Professor C. E. A. Winslow, of Yale, said in a public address about fifteen years ago: "In this whole first phase of practical disease control in the United States, William F. Snow was the stage manager, even though he rarely occupied the limelight in his own person." Dr. Maurice A. Bigelow, in a short biographical sketch which accompanied invitations to a commemorative dinner to Dr. Snow in 1937, said of the same period: "The amount of labour he performed was colossal. He seemed to be driven by some high-compression engine denied to other men. In fact his nickname was 'Driven Snow.'"

From 1924 to 1928 Dr. Snow was chairman of the League of Nations Committee to Study the Traffic in Women and Children, and from 1947 until his death he was president of the Union Internationale Contre le Péril Vénérien. Besides these offices he held many others, as professor or lecturer in preventive medicine in different universities, as chairman of various bodies interested in public health, or as adviser to the U.S. Public Health Department. All his work was actuated by the principles of preventing infection through education, medical care, the wholesome occupation of leisure, and the repression of commercial prostitution. The affection and esteem of his associates were well expressed at a dinner in New York on October 1, 1937, when over 400 guests met to present him with a bronze portrait plaque, "on the occasion of his fortieth year of distinguished service to education, public health, and social hygiene." Many speakers, including the late Sir Arthur Newsholme, testified to Dr. Snow's courage, energy, and single-minded honesty of purpose. The speeches made at this dinner were published in a souvenir number of the *Journal of Social Hygiene* in December of that year. To the writer of the present tribute it was comforting to find that all expressed in effect the spirit of his own contribution to the symposium:

"It was high time that Dr. Snow was dragged into the limelight, so that he may feel the esteem in which those best qualified to judge his work hold him, and a wider public may learn something of what society owes him for the great part he has played in the campaign against venereal diseases and the traffic in women and children. Just before I first met Dr. Snow, at the birth of the League of Red Cross Societies in Cannes in 1919, I heard one of the American leaders speak of him as a man who, in the long run, achieved his objective, whatever the obstacles, without fuss and often without anyone being conscious of the solvent process that had been at work on the opposition. I think events have shown that judgment to have been pretty correct. Snow and I, with such distinguished men as Roux and Ducrey, were members of the V.D. Committee of that Red Cross Conference at Cannes, and it ended in the two of us drafting the resolutions. At least Snow did the work, and I, knowing that he would get his own way about them eventually, meekly agreed. It must be very gratifying to him and to you all, his associates in the fight you have waged so long against V.D. in America, to see its importance being recognized at long last by the general public."

In the years since then nothing has occurred to alter those sentiments. It may be added that Dr. Edward L. Keyes, the distinguished urologist, in presenting the plaque, said: "I have been asked, my dear Dr. Snow, to present this plaque to the most modest and the most diplomatic man I know." Dr. Snow is survived by his widow and two sons.—L. W. H.

Professor Fred Grundy writes: William Freeman Snow was known to me for many years as chairman of the Board of Directors of the American Social Hygiene Association, the American counterpart of the British Social Hygiene Council, of which I am myself chairman. He was probably best known to his medical colleagues in the United States and to many medical and social workers in the four quarters of the globe as one of the outstanding figures in the field of international medicine concerned with the prevention of venereal diseases. It is not for me to comment on Snow's special contribution to an important but unspectacular aspect of preventive medicine which rarely attracts the acclamation it deserves, but I would like to say a word about Snow as a man. I first made his aquaintance some years ago in New York, and less than two years ago, along with Colonel L. W. Harrison, we spent a few happy hours together in London, hours which he had contrived to snatch from a full programme of international conferences on the European mainland. William Freeman Snow was a quiet unassuming personality, liked and respected by all who knew him. He was a good friend, completely honest in his professional dealings and the opinions he expressed, and

always ready to put his wide experience at the disposal of anyone who sought his counsel; and, above all, always ready to extend a practical helping hand to anyone who needed it. Particularly, like so many of his professional colleagues in the United States, he spared no effort to smooth the way for visitors from this side of the Atlantic to New York and other medical centres in the States. Snow will be missed and mourned by his friends and colleagues of many countries, and his name will be remembered for a life of service in a humanitarian field which transcends national boundaries.

Dr. KENNETH ARLY PORTERFIELD RYND MURRAY, of Surbiton, was taken ill suddenly while driving his car near Leatherhead. He was taken to the hospital there and he died on April 9. Dr. Murray, who was 66, and qualified in 1908, had been in practice at Surbiton for the last seventeen years. His genial manner had endeared him to many friends, and his invariable kindness and courtesy won him the affection of his patients. During the 1914–18 war he served in the R.A.M.C. and was attached to the 48th Midland Brigade Field Ambulance. He was awarded the Military Cross in 1918 for rescuing wounded under heavy fire. Dr. Murray's sudden and untimely death will be mourned by many friends and colleagues in Surbiton, and their sympathy will be extended to his widow. His only son, a sub-lieutenant in the Royal Navy, was killed in H.M.S. *Gloucester* in 1940.

Dr. MORRIS YOUDELEVITZ YOUNG, who died in London on May 18, at the age of 68, was a notable figure. Graduating M.B., Ch.B. in Glasgow in 1906, he went to Persia the following year with the D'Arcy Exploration Company and remained there for the next 20 years with the Anglo-Persian Oil Company, which developed from the D'Arcy group. He built up the extensive medical service of that company. In the early days when money was short every item of medical advancement had to be fought for, but by perseverance and wise spending he had built up a remarkable hospital and medical system by the time he left the country for good in 1926. He retired in 1933 from the post of Chief Medical Officer of the Anglo-Iranian Oil Company but continued as the company's medical adviser. Young was a remarkable linguist, fluent and idiomatic in Arabic, Persian, Hebrew, and French, and his services were often used by the oil company in matters which were far from medical in character. He had staunch friends among the wild tribesmen, often because of medical kindnesses rendered to them, and with their chieftains he was more than once able to effect agreements and obtain pledges which would not have been given to anyone else. At first transport was of the most primitive kind, and he made long journeys on his missions undeterred by the hardest conditions. Of very small stature, he was a dynamo of energy, and the diminutive figure of the "Wee Doctor," always in a hurry and always talking in some strange language, became a legend known the length and breadth of Persia. In the 1914–18 war Young's services were very valuable to the Government in combating German infiltration in Persia, and he was made a C.I.E. in 1917. Once during this phase he was a victim of the method of poisoning so often used in those parts and he just escaped with his life after days of delirium. In England after his retirement Young gave himself up almost entirely to bacteriological research with Sir Almroth Wright and Sir Alexander Fleming, always as a voluntary worker. Both leant heavily on him for help, not only in the laboratory but in the committee room, where his administrative experience, organizing ability, and clear sight were invaluable. Young leaves behind him a host of friends and thousands who bless his name for his never-failing kindness and care in times of illness and adversity.—A. D. W.

Dr. ALFRED EDWARD ARTHUR CARVER, the medical director of Caldecote Hall, Nuneaton, died on May 30 at the age of 65 after a long illness. Dr. Carver was the son of the Rev. Arthur Wellington Carver, Vicar of Langton, and a grandson of the Rev. Dr. Alfred James Carver, Master of Dulwich. He was educated at Caius College, Cambridge, and St. Bartholomew's Hospital. He took the conjoint diploma in 1908 and later graduated M.B., Ch.B., proceeding M.D. in 1914. He took the Oxford D.P.H. in 1915 and the Cambridge D.P.M. in 1919. His academic career was interrupted by the 1914–18 war, when he served with the 36th General Hospital in Salonika. From 1917 he was the neurological specialist at the big German prisoner-of-war camp at Cannock Chase. Dr. Carver studied in Vienna under Professor Freud, and on returning to this country was for a time assistant neurologist at the Maghull Special Hospital. He was in charge of the Psychotherapeutic Clinic of the Birmingham and Midland Hospital for Diseases of the Nervous System. His interest in psychology and psychiatry, on both of which subjects he wrote many papers, led finally to his appointment as medical director of Caldecote Hall. This was established under the auspices of the Church of England Temperance Society, of which Dr. Carver was a permanent member. During the war Caldecote was one of the special neurosis centres under the E.M.S., and the heavy responsibilities which Dr. Carver already carried were greatly increased at that time. Dr. Carver was particularly interested in alcoholism and in drug addiction, and during his 25 years there he built up a considerable reputation for Caldecote Hall. The sympathy of his colleagues and many friends will be extended to his widow, who survives him with two sons. The third son, a captain in the 7th Gurkha Regiment, was killed in action in 1942.

Medical Notes in Parliament

Merit Awards for Consultants

Mr. CHARLES TAYLOR asked the Minister of Health on June 15 when he expected to receive the report of the committee now considering merit awards for medical consultants.

Mr. BEVAN said that he expected to receive a report within the next three months. Mr. TAYLOR then asked was it not intolerable that this class of consultant should be left in such a state of uncertainty for so long.

Mr. BEVAN said this was entirely a professional matter. It had not been determined by him at all. It would have been even more intolerable if, by hasty action, the wrong people had been selected.

Col. STODDART-SCOTT asked how long had this committee been sitting, who was its chairman, and what was the salary paid to him for a year. Mr. BEVAN said that if the question was put down he would try to answer it.

Senior Hospital Medical Officers

Dr. REGINALD BENNETT, also on June 15, asked the Minister of Health to what extent medical officers graded senior hospital medical officer were thereby rendered ineligible for promotion to consultant status.

Mr. BEVAN replied "Not at all," but did not make any further comment when Dr. BENNETT went on to ask if he agreed that the interpolation of this grade between the grade of senior registrar and that of consultant looked extraordinarily like a device for obtaining the services of specialists at cut rates.

Voeller's Treatment for Parkinsonism

Mr. JOHN ARBUTHNOT asked the Minister of Health whether he was yet in a position to make a statement on Dr. Voeller's treatment for Parkinson's disease; and, if not, when he expected to be in a position to do so, bearing in mind the length of time he had had the report.

Mr. BEVAN said that the group of patients who went to this clinic under observation had now been re-examined a year

a.:er their treatment began. He was advised that the methods used by Dr. Voeller combined an intensive rehabilitation course with drug treatment and diet. These methods did not constitute a cure, nor did they introduce any new principles, but in the small sample of cases investigated they modified with varying degrees of success the steady deterioration which was the normal progress of the disease, and encouraged patients to continue their own efforts to improve.

Research on Muscular Dystrophy

Mr. TURTON asked the Lord President of the Council how many persons had been diagnosed as suffering from muscular dystrophy in the last five years and what research was being conducted into this disease.

Mr. HERBERT MORRISON said that the figures were not available. Research on the muscular dystrophies formed an important part of the work of the Medical Research Council's Neurological Research Unit at the National Hospital, Queen Square, London.

Sir RICHARD ACLAND asked if it would be possible to indicate the volume of research being carried on, for example, by saying how much it cost for 12 months.

Mr. MORRISON said no. Members were repeatedly wanting to know how much these things cost, as though that were an accurate measure of successful research. Research could not be measured by money. Brains came into it as well.

Anthrax.—In England, according to the Minister of Agriculture, there were 108 outbreaks of anthrax in 1947, 95 in 1948, and 204 in 1949, and there have been 149 so far this year. Although outbreaks have occurred in the majority of counties they have been most numerous this year in Lancashire and the West Riding of Yorkshire. It is probable that the increased incidence of anthrax is due largely to the increased imports of fertilizers and animal feeding-stuffs from abroad.

Medico-Legal

DERMATITIS FROM HAIR DYE

Appeal Succeeds

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

We recently published a short account of an action in the High Court in which Mr. Justice Croom Johnson awarded £600 damages to a lady who had suffered from dermatitis after a treatment by a hairdresser with "Inecto Rapid" hair dye.[1] The hairdresser said he had known that the dye was dangerous and had warned the customer, but the judge rejected that evidence and found that he had broken his contract to sell her a dye fit for the purpose for which she had bought it. He found the manufacturers, Messrs. Rapidol, guilty of negligence, because, he said, the warning they had given on their packages and in the booklet supplied with the dye had been insufficient and ambiguous.

The Court of Appeal, however, allowed an appeal by the manufacturers. Lord Justice Tucker, giving the court's judgment,[2] said that he saw no reason for rejecting the evidence of the hairdresser, who had said that he had read the warning and appreciated what it meant. It was therefore impossible to hold that the warning had been insufficient, and it would be unreasonable to expect the manufacturers to give warning in such a form that it must come to the knowledge of the customer who was going to be treated. The manufacturers were awarded the costs of the previous action, but did not ask for the costs of the appeal.

[1] *British Medical Journal*, April 15, 1950, p. 911.
[2] *Manchester Guardian*, May 10, 1950.

Universities and Colleges

UNIVERSITY OF OXFORD

In a Congregation held on June 3 the following degrees were conferred:

D.M.—J. M. Rice-Oxley, J. R. O'Brien.

UNIVERSITY OF CAMBRIDGE

In Congregation on June 8 the honorary degree of D.Sc. was conferred on William Shainline Middleton, Hon.C.B.E., M.D., F.R.C.P., President of the American College of Physicians and Dean of the Medical School of the University of Wisconsin. The honorary degree of D.Litt was conferred on Mr. Stanley Morison, who was largely responsible for the complete change of type-face undertaken by *The Times* in the latter part of 1932 and upon whose recommendation the same type has been used for the *British Medical Journal* since the beginning of 1937.

R. H. Winfield, M.B., B.Chir., has been appointed a member of the committee of management of the Scott Polar Research Institute until December 31, 1953.

The degree of M.D. was conferred on A. G. E. Pearse and A. Miller on June 10.

UNIVERSITY OF EDINBURGH

The Dean of the Faculty of Medicine of the University has announced that the Wellcome Medal and Prize in the History of Medicine will be awarded in July, 1951, for the best essay on "Hippocrates in the Light of Modern Medicine." The value of the prize is £25. Competitors must have been members of the University Class of the History of Medicine within a period of five years preceding the date of award. Essays must be lodged with the Dean of the Faculty of Medicine on or before May 1, 1951.

The Wellcome Medal and Prize for 1950 has been awarded to Dr. H. P. Tait for his essay on "The Early History of Paediatrics" and will be presented to him at the Graduation Ceremonial on July 19.

UNIVERSITY OF LONDON

The title of Professor of Pharmacology in the University has been conferred on John Michael Robson, D.Sc., M.D., in respect of the post held by him at Guy's Hospital Medical School.

UNIVERSITY OF WALES

The following candidates for the degrees of M.B., B.Ch. at the Welsh National School of Medicine have satisfied the examiners at the examinations indicated:

SURGERY.—S. I. Davies, *D. W. Evans, A. R. Harris, A. J. Hooper, J. I. Hopkins, T. M. Morgan, T. L. Morris, S. J. S. Polwin, Margaret Pugh, Dilys Rees, J. W. Rees, T. A. I. Rees, D. B. Scourfield, A. P. Thomas.

PHARMACOLOGY.—R. F. Addy, G. V. Browning, Gillian M. Bryant, H. G. Burgess, A. Capstick, Jean E. Clarke, Marian H. Dadaczynski, Marian W. Daniel, E. G. Davies, H. L. S. Davies, Jean M. Davies, Barbara C. Edwards, D. G. Edwards, Barbara M. Evans, Betty Evans, D. L. Evans, Mary E. Ll. Evans, D. W. Foster, Beryl A. Foulger, T. Gunner, Felicity Harris, G. B. Harris, G. Harry, W. R. Henwood, D. R. Hughes, J. Hughes, A. P. Jones, Betty R. Jones, B. Jones, J. F. Jones, T. L. Jones, Margaret Land, D. N. D. Lewis, G. P. Lewis, J. E. Lloyd, Dorothy J. Luck, A. D. Mason, K. C. Parsons, E. B. Phillips, J. Quirk, Edna Rees, O. S. Roath, G. H. Roberts, J. Roberts, Hilda Rosenthal, R. W. Shepherd, A. O. Thomas, Phyllis M. Thomas, I. P. Vaughan, Margaret M. Walker, J. E. Watkin, Elfreda A. Watkins, D. J. Ll. Williams, Elizabeth M. M. Williams, Meriel Williams.

*With distinction.

UNIVERSITY OF SHEFFIELD

The following appointments are announced: *Full-time Demonstrators in Anatomy*, E. J. Clegg, M.B., Ch.B., J. A. Howarth, M.B., Ch.B., and F. R. Johnson, M.D. *Part-time Clinical Teacher in Department of Medicine*, H. F. West, M.D., M.R.C.P., D.T.M. *Part-time Tutor in Obstetrics and Gynaecology*, J. G. Napier, M.B., F.R.C.S.Ed., M.R.C.O.G.

A circular from the Ministry of Health reminds hospital boards and committees that they should not employ nurses and midwives whose terms of service, and in particular remuneration, differ from those agreed through the Whitley Council. In exceptional circumstances the Minister may authorize their employment at special rates.

No. 22

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended June 3.

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland. (d) Eire. (e) Northern Ireland.
Figures of Births and Deaths, and of Deaths recorded under each Infectious disease, are for: (a) The 126 great towns in England and Wales (including London). (b) London (administrative county). (c) The 16 principal towns in Scotland. (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland.
A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

Disease	1950 (a)	(b)	(c)	(d)	(e)	1949 (Corresponding Week) (a)	(b)	(c)	(d)	(e)
Meningococcal infection	36	1	22	—	1	39	5	16	2	1
Deaths		—	—				—	—		
Diphtheria	45	3	21	3	4	100	14	23	3	3
Deaths	—	—	—	—	—	1	—	—	—	1
Dysentery	454	25	134	—	1	85	4	40	—	—
Deaths					—				—	—
Encephalitis, acute	6	2	—		—	2	—	1	—	—
Deaths		—		—			—			
Erysipelas			21	12	5			22	11	3
Deaths							—			
Infective enteritis or diarrhoea under 2 years				17					43	
Deaths	11		4	3	1	19	4	2	6	—
Measles*	10,075	478	980	250	172	9,583	953	597	239	180
Deaths†		—	4	1	—					
Ophthalmia neonatorum	29	3	12		1	50	7	7	—	—
Deaths										
Paratyphoid fever	5	—	—		—	8	—	1 (B)	—	—
Deaths	—		—		—	—	—	—	—	—
Pneumonia, influenzal	458	21	7	—	2	485	30	5	4	6
Deaths (from influenza)‡	7	—	—	1	—	10	2	—	1	—
Pneumonia, primary			180	¶			•	165	37	
Deaths	142	18		4	5	156	28		8	8
Poliomyelitis, acute	37	3	3	5	3	20	1	1	—	1
Deaths§	1	—		—		—	—			
Puerperal fever		—	7				—	7		
Deaths										
Puerperal pyrexia‖	63	7	18	—	—	102	11	2	—	3
Deaths							—			
Relapsing fever	—	—			—	—	—			—
Deaths										
Scarlet fever	1,158	88	151	72	54	1,233	80	189	75	25
Deaths†			—	—	—			—	—	—
Smallpox	—	—	—		—	—	—	—	—	—
Deaths					—				—	—
Typhoid fever	3	—	3	6	2	4	—	—	3	—
Deaths	—	—	—		—	1	1	—	—	—
Typhus fever	—	—	—	—	—	—	—	—	1	—
Deaths					—				—	—
Whooping-cough	2,613	139	335	75	47	2,611	141	163	114	71
Deaths	5	1	1	1	—	9	—	1	3	—
Deaths (0–1 year)	225	26	31	15	6	268	28	40	22	12
Deaths (excluding stillbirths)	4,357	623	627	169	94	4,330	631	592	179	111
Annual death rate (per 1,000 persons living)			12·6					11·9	11·1	
Live births	6,781	1159	931	443	244	7,930	1269	1024	341	273
Annual rate per 1,000 persons living			18·7					20·5	21·1	
Stillbirths	162	15	29			220	23	32		
Rate per 1,000 total births (including stillborn)			30					30		

* Measles is not notifiable in Scotland, and the returns are therefore an approximation only.
† Deaths from measles and scarlet fever for England and Wales, London (administrative county), will no longer be published.
‡ Includes primary form for England and Wales, London (administrative county), and Northern Ireland.
§ The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, London (administrative county), are combined.
‖ Includes puerperal fever for England and Wales and Eire.
¶ Primary pneumonia no longer notifiable in Eire.

EPIDEMIOLOGICAL NOTES

Poliomyelitis in England and Wales

In the week ended June 10 there were 79 (37) notifications of poliomyelitis, 61 (27) paralytic cases, and 18 (10) non-paralytic. Figures for the previous week are shown in parentheses, and it will be seen that they were slightly less than one-half of those for the twenty-third week. In the twenty-first week notifications numbered 50 (34 paralytic cases and 16 non-paralytic). The geographical distribution shows a marked preponderance of cases in the Midlands, with 22 notifications in Warwickshire and 9 in Staffordshire.

This rise in notifications has come earlier than usual, and 79 notifications is probably the highest figure ever recorded in a twenty-third week. It is not possible to be certain on this point, since the change in categories of notification introduced in 1950 makes exact comparisons with previous years impossible. It is too early to hazard a guess whether this early rise presages an incidence of the order seen in 1947 and 1949, or whether the experience of 1948 is more likely to be repeated. In 1948 there was no clear-cut epidemic, but the curve of summer and autumn prevalence was a prolonged and flattened one. The incidence rose to 31 cases in the twenty-fifth week of 1948 and remained between about 30 and 45 cases until the thirty-third week, when it rose to 78, and remained at about that level until the forty-fourth week, when it slowly declined.

Food-poisoning in North Staffordshire

An outbreak of food-poisoning occurred in a semi-urban area in North Staffordshire on June 4. The occasion was a birthday party, which was celebrated by a high tea. Of 34 people present 15 became ill within two to five hours. The onset was sudden and acute, with vomiting, diarrhoea, abdominal pain, and marked prostration. The symptoms were most severe among the young (2 years) and the old (70–74 years), but all had to be admitted to hospital. There were no deaths, and complete recovery occurred in the majority within 36 to 48 hours.

Samples of the various articles of food consumed were available for investigation, and of these the pressed tongue was found to be heavily infected with coagulase-positive *Staphylococcus aureus*. The chief operator in the processing of the tongue was found to be a heavy nasal carrier of this organism, and subcultures of organisms obtained from him, from the tongue, and from the vomit of three patients were all reported by the Central Public Health Laboratory at Colindale to be of the same phage type.

In addition to the tongue presumed to have been the vehicle of infection, two other tongues were processed on the same day, June 1, at the butcher's shop. These were kept in a refrigerator until June 3, when they were delivered to a working men's club, and kept in a refrigerator there until eaten on the same day. A large number of people partook of these tongues, but only two seem to have suffered from symptoms of food-poisoning (moderately severe). On the other hand, the tongue issued on June 2 to the establishment where the birthday party was held was not put into a refrigerator and was consumed on June 4.

Discussion of Table

In *England and Wales* decreases were reported in the notifications of whooping-cough 353, scarlet fever 137, acute pneumonia 31, and diphtheria 15. There was a rise in the incidence of measles 721.

The largest falls in the notifications of whooping-cough were Yorkshire West Riding 108, Lancashire 67, and Warwickshire 56. A small decrease was recorded in the incidence of scarlet fever in most areas of the country.

The largest fluctuations in the local returns of measles were rises in the notifications in Northumberland 208, Yorkshire West Riding 134, Suffolk 129, Gloucestershire 89, and Hertfordshire 86, with falls in Lincolnshire 88, Lancashire 85, and Durham 74. The only variation of any size in the local trends of diphtheria was a decrease of 5 in Durham.

Notifications of dysentery were 3 fewer than in the preceding week. The chief feature of the returns was a decrease of 92 in Yorkshire West Riding and an increase of 101 in Lancashire. The largest returns were Lancashire 180 (Oldham C.B. 78, Chadderton U.D. 32, Crompton U.D. 18, Manchester C.B. 18, Burnley C.B. 16, Preston C.B. 9); Yorkshire West Riding 77 (Sheffield C.B. 13, Bradford C.B. 12, Queensbury and Shelf U.D. 12); Durham 43 (Stanley U.D. 21, South Shields C.B. 7, Lancaster R.D. 6); London 25 (Wandsworth 6); Staffordshire 19 (Smethwick C.B. 18); Denbighshire 16 (Aled R.D. 16); Yorkshire North Riding 14 (Northallerton R.D. 9, Middlesbrough C.B. 5); and Yorkshire East Riding 11 (Kingston-upon-Hull C.B. 11).

A further 7 cases of acute poliomyelitis were notified from the outbreak in Birmingham C.B., but no further cases were reported from the outbreak in Staffordshire. The largest outbreak of food-poisoning notified was Suffolk, Thingoe R.D. 55.

In *Scotland* increases were recorded in the notifications of measles 255, dysentery 23, and acute primary pneumonia 14, with decreases in the incidence of whooping-cough 37 and scarlet fever 16. The largest returns of dysentery were Glasgow 69, Dundee 29, Edinburgh 15, and Lanarkshire county 10. A small decrease in the incidence of scarlet fever occurred throughout the country, except in the Western area.

In *Eire* an increase was reported in the notifications of measles 26 and a decrease of 12 for scarlet fever. The fall in the incidence of scarlet fever was due to the experience of Dublin C.B. An outbreak of measles with 32 cases was notified in Longford, Grandard, No. 1 R.D., and a further 49 cases were notified in the outbreak in Dublin, Dun Laoghaire U.D.

In *Northern Ireland* a decrease of 17 in the notifications of scarlet fever was the only fluctuation of any size in the trends of infectious diseases; there were falls of 8 in Belfast C.B. and in County Armagh, with a rise of 14 in County Down.

Week Ending June 10

Notifications of infectious diseases in England and Wales during the week included: scarlet fever 846, whooping-cough 3,437, diphtheria 73, measles 10,712, acute pneumonia 480, acute poliomyelitis 79, dysentery 353, paratyphoid fever 7, typhoid fever 9. One case of typhus was imported.

Medical News

Beit Memorial Fellowships Report

According to the report of the trustees of the Beit Memorial Fellowships for medical research for the year 1949–50 the trustees noted with great satisfaction that during the year two of their former Fellows—Professor M. Stacey (1933–6) and Professor R. J. Pumphrey (1936–9) had been elected to the Fellowship of the Royal Society. The following elections were made: Fourth Year Fellowship (value £700 a year): Mr. G. Weber, Ph.D., to study the dissociation of insulin, at the School of Biochemistry, University of Cambridge. Junior Fellowships (normal value £600 a year): Mr. J. Crossland, M.A., to study the nature and functions of humoral factors in nervous transmission in the brain, at the Neuropsychiatric Research Centre, Whitchurch Hospital, Cardiff; Dr. Joan E. Keilin, to study the link between the haem and protein in haemoglobin, at the School of Biochemistry, Cambridge; Mr. R. J. Salton, Bac.Agric.Sc., Sydney, to study the chemical and immunological nature of the outer envelopes of bacterial cells, at the Department of Colloid Science, Cambridge.

Edward Nettleship Prize

The council of the Ophthalmological Society of the United Kingdom announces that the Edward Nettleship prize for 1950 has been awarded to Professor A. J. Ballantyne.

Wellcome Historical Exhibition Catalogue

An illustrated catalogue of the exhibition at the Wellcome Historical Museum depicting "Medicine in 1850" has been issued. In an introduction Dr. E. Ashworth Underwood, director of the museum, draws attention to some of the outstanding events in the history of medicine in the nineteenth century, the middle of which "was indeed a golden age for the physician." The catalogue includes many interesting historical notes on the exhibits, and is in itself a small conspectus of nineteenth century medical history. It is published by the Oxford University Press, and is obtainable for 3s. from the publishers or from booksellers. The exhibition was described in the *Journal* of May 27 (p. 1258).

New Under-Secretary for Finance

The Minister of Health has approved the appointment of Mr. F. L. Edwards to the post of Under-Secretary for Finance and Accountant-General in the Ministry of Health, in succession to Mr. H. H. George, who is retiring from the public service on July 5.

Kathleen Schlesinger Fellowship

The Medical Research Council invites applications for the Kathleen Schlesinger Fellowship. This fellowship is provided from a fund established by the late Mr. E. M. Schlesinger and Mrs. Schlesinger in memory of their daughter. It will be awarded by the council, under the terms of the trust deed, to a suitably qualified person who will devote his or her whole time to "investigating the origin and nature of cysts of the brain, whether arising from tumours or not, or to such studies of other conditions of the central nervous system as the council may from time to time permit." With this object in view, preference will be given to candidates who elect to work on the mechanisms underlying degenerative processes affecting the brain. The fellowship will ordinarily be tenable at the National Hospital for Diseases of the Nervous System, Queen Square, London, and for a period of one year in the first instance, renewable annually up to a maximum of three years in all. The stipend will be within the range £700 to £1,000 per annum, according to qualifications and research experience. Applications, giving full personal particulars, an outline of the proposed research, and the names of two referees, should be lodged with the Secretary, Medical Research Council, 38, Old Queen Street, London, S.W.1, not later than July 15.

Minister of Health for India

Several members of the Cabinet and a large number of medical men, eminent in their various spheres, attended a luncheon given on June 14 by the High Commissioner for India in honour of Rajkumari Amrit Kaur, Minister of Health for India. Rajkumari Amrit Kaur was on a brief visit to this country after attending the General Assembly of the World Health Organization, of which she is President for the coming year. As Mr. Aneurin Bevan explained at the lunch, certain things had befallen which prevented him from accepting the invitation of the Government of India to visit India to advise them on the problems of a health service for that country. Rajkumari Amrit Kaur said that she was therefore paying a visit to London in order to learn something about the National Health Service before her return to India. She thought that the British experiment would serve as a model for the rest of the world, and hoped that the ties between India and Britain, where she had spent many happy years of her life, would become closer as the years went by.

Medical Auxiliaries

Mr. L. V. Cargill, F.R.C.S., treasurer and a vice-president of the Board of Registration of Medical Auxiliaries since 1937, has retired. Mr. J. H. Hanby, F.Ch.S., has been appointed treasurer, and Dr. A. P. Gibbons and Mr. F. Melville vice-presidents. Dr. S. Howitt has been appointed by the Society of Apothecaries to replace Mr. Cargill.

New Journal of Cytology

The International Society for Cell Biology has started publication of a journal entitled *Experimental Cell Research*, the first number of which was dated January, 1950. Four issues will be published a year for 10 dollars. Orders should be sent to the Academic Press Inc., 125 East 23rd Street, New York, 10, U.S.A. The British member of the editorial board is Dr. Honor B. Fell, Strangeways Research Laboratory, Cambridge, to whom authors resident in Britain should submit their manuscripts. The journal will publish papers dealing with the experimental analysis of the activity, structure, and organization of the cell and its subunits, and also on virus research. Technical or theoretical papers on the development of methods in experimental cytology will also be acceptable.

COMING EVENTS

British Association of Urological Surgeons

The British Association of Urological Surgeons will hold its Sixth Annual Meeting at Manchester on June 30 to July 1. Full particulars may be obtained from the association at 45, Lincoln's Inn Fields, London, W.C.2.

British Standards Institution

The annual general meeting of the British Standards Institution will be held on Tuesday, July 11, at 3 p.m., in the Council Room of the institution at 24, Victoria Street, London, S.W.1.

Consultants and Specialists Meeting

The annual general meeting of all consultants and specialists (including those graded S.H.M.O.) in contract with the Regional Hospital Board and the Board of Governors of the Sheffield Region will be held at Pearson House, Nottingham General Hospital, on Saturday, July 8, at 3 p.m.

Italian Medical Meeting

Papers on a variety of medical subjects will be read at a meeting to be held at Verona on July 20–30. Particulars may be obtained from the Giornate Mediche Internazionali, Minerva Medica, Torino, Italy.

Preventive Medicine in South Wales

A conference on preventive medicine in South Wales will be held by the South Wales Branch of the Socialist Medical Association at the Y.M.C.A. Hostel, Rhoose, near Barry, on Sunday, July 2. Particulars may be obtained from Mr. L. R. Fletcher, National Council of Labour Colleges, 321, Cowbridge Road, Cardiff.

SOCIETIES AND LECTURES

A fee is charged for attending lectures marked ●. Application should be made first to the institution concerned.

Saturday

SCOTTISH SOCIETY OF THE HISTORY OF MEDICINE.—At Royal Society of Edinburgh, June 24, 10.45 a.m., papers by Professor R. H. Shryock (Baltimore) and Professor Whitfield Bell (Philadelphia); 2 p.m., pilgrimage to grave of William Cullen, birthplace of Robert Liston, and Priory of Torphichen.

Monday

INSTITUTE OF NEUROLOGY: NATIONAL HOSPITAL, Queen Square, London, W.C.—June 26, 5 p.m., *"Pott's Paraplegia,"* by Mr. H. J. Seddon.

MEDICAL RESEARCH COUNCIL.—At London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., June 26, 5.15 p.m., *"Transfer of Heat and of Vapour Through Clothing,"* by Professor A. C. Burton, Ph.D. (University of Western Ontario).

UNIVERSITY COLLEGE (Physiology Theatre), Gower Street, London, W.C.—June 26, 4.45 p.m., *"Genetics and Biochemistry,"* by Professor J. B. S. Haldane, F.R.S.

Tuesday

INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—June 27, 5 p.m., *"Matters Relating to Occupational Dermatoses,"* by Dr. R. M. B. MacKenna.

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—June 27, 5.30 p.m., *"Standards of Lighting and Visual Hygiene,"* by Mr. H. C. Weston.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, London, W.C., June 27, 5.30 p.m., *"Some Recent Studies of Porphyrin Metabolism and Porphyria,"* by Professor C. J. Watson (University of Minnesota).

PADDINGTON MEDICAL SOCIETY.—At St. Mary's Hospital, Paddington, London, W., June 27, 8.45 p.m., annual general meeting. *"Some Problems of General Practice,"* discussion to be opened by Dr. L. Zeitline.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—June 27, 5 p.m., *"Current Trends in the Surgical Management of Lesions of the Colon,"* Hunterian Lecture by Dr. Arthur W. Allen.

ROYAL EYE HOSPITAL, St. George's Circus, London, S.E.—June 27, 4.15 p.m., *"Contact Lenses."* by Dr. C. G. Kay Sharp.

Wednesday

INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—June 28, 5 p.m., *"Biochemistry,"* by Dr. J. O. Oliver.

MEDICAL RESEARCH COUNCIL.—At London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., June 28, 5.15 p.m., *"The Science of Field Testing,"* by Professor A. C. Burton, Ph.D. (University of Western Ontario).

ROYAL EYE HOSPITAL, St. George's Circus, London, S.E.—June 28, 5.30 p.m., *"The Facies in Disease,"* by Mr. L. H. Savin.

Thursday

DREADNOUGHT SEAMEN'S HOSPITAL, Greenwich, S.E.—June 29, 3 p.m., demonstration of surgical cases by Mr. Stephen Power. All medical practitioners interested are invited.

FACULTY OF HOMOEOPATHY.—At Royal London Homoeopathic Hospital, Great Ormond Street, London, W.C., June 29, 5 p.m., *"The Clinical Uses of Electroencephalography,"* by Dr. G. Pampligione (Bologna).

HARVEIAN SOCIETY OF LONDON.—At Grocers' Hall, Princes Street, London, E.C., June 29, 7 for 7.30 p.m., The Buckston-Browne-Gray-Hill Dinner.

INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—June 29, 5 p.m., *"Vitamin-A Deficiency and the Skin,"* by Dr. A. D. Porter.

INSTITUTE OF NEUROLOGY: NATIONAL HOSPITAL, Queen Square, London, W.C.—June 29, 5 p.m., *"Neurosurgical Aspects of Vascular Diseases,"* by Dr. Ludo Van Bogaert (Antwerp).

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—June 29, 5.30 p.m., *"Referred Pain,"* by Dr. D. Slome.

ROYAL EYE HOSPITAL, St. George's Circus, London, S.E.—June 29, 5.30 p.m., *"Toxoplasmosis,"* by Mr. R. P. Crick.

ROYAL SOCIETY, Burlington House, Piccadilly, London, W.—June 29, 4.30 p.m., *"Growth and Plasticity in the Nervous System,"* Ferrier Lecture by Professor J. Z. Young, F.R.S.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—June 29, 4.30 p.m., *"Psychiatry,"* lecture-demonstration by Dr. M. A. Partridge.

Friday

MAIDA VALE HOSPITAL FOR NERVOUS DISEASES MEDICAL SCHOOL, Maida Vale, London, W.—June 30, 5 p.m., clinical neurological demonstration, by Dr. Helen Dimsdale.

WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At West London Hospital, Hammersmith, London, W., June 30, 6 p.m., annual general meeting.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Davidson.—On May 27, 1950, at Wendover, Bucks, to Veronica, wife of John H. Davidson, M.B., B.S., Squadron Leader, R.A.F., a daughter.

Carlile.—On May 28, 1950, to June (formerly Hillary), wife of Dr. J. P. Carlile, of 467, Earlham Road, Norwich, a daughter.

Clark.—On June 6, 1950, at Rubislaw Nursing Home, Aberdeen, to Constance (formerly Eames), wife of Norman S. Clark, M.B., Ch.B., M.R.C.P., a daughter.

Eason.—On May 21, 1950, at Lambeth Hospital, London, S.E., to Ruth Eason (formerly Towler), M.B., Ch.B., wife of Thomas John Eason, F.R.C.S., a son.

Jarratt.—On June 8, 1950, at King's College Hospital, Denmark Hill, London, S.E., to Mary (formerly O'Keeffe), wife of Dr. E. W. Jarratt, a daughter.

Lester.—On June 16, 1950, at Solihull, Birmingham, to Mary, wife of Mr. Stephen Lester, F.R.C.S.Ed., a son.

Ormrod.—On June 12, 1950, at Boney Hay, Walsall, to Iris, wife of Peter Ormrod, M.R.C.S., L.R.C.P., a son.

Pitt.—On June 13, 1950, at Watford Maternity Home, to Penelope (formerly Reynolds), wife of Dr. Peter Pitt, a daughter.

Winter.—On May 31, 1950, in Bristol, to Mollie, wife of Dr. George Winter, a son—John James.

MARRIAGE

Howe—Schubert.—On June 17, 1950, at Zurich, Switzerland, Marcus Slade Howe, *M.C.*, M.R.C.S., L.R.C.P., D.A., of St. Leonards-on-Sea, Sussex, to Eva Erika Schubert, of Zurich, Switzerland.

DEATHS

Biddle.—On June 7, 1950, at Stradbroke, Diss, Norfolk, Henry George Biddle, M.R.C.S., L.R.C.P., aged 83.

Turner.—On May 27, 1950, at a York nursing-home, Henry William Turner, M.C., L.R.C.P.&S.Ed., L.R.F.P.S.Glas., of The Grange, Welburn, York.

Walla.—On May 23, 1950, in London, Sohrab Hodi Walla, L.R.C.P.&S.Ed., L.R.F.P.S.Glas., D.P.H., of 6, Castelnau Mansions, Barnes, London, S.W., formerly of Fulham Palace Road, London, S.W., aged 65.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Tuberculous Endometritis and Salpingitis

Q.—*How should one treat a case of tuberculous endometritis, proved by biopsy, with tuberculous involvement of the right Fallopian tube? There is a well-healed focus at the apex of the right lung and the patient seems otherwise to be in good health. Is conservative or radical treatment called for, and what advice should be given about marriage?*

A.—If it can be assumed that active disease, not only in the lungs but elsewhere, has been excluded, this type of case constitutes one of the great problems in modern gynaecological practice, and opinion on treatment is divided. If there is no history of tuberculous peritonitis in the past, and if the pelvic organs are reasonably mobile, the writer's view is that laparotomy should be carried out with a view to total hysterectomy and bilateral salpingectomy. It is usually possible to conserve at least one ovary. As an alternative there would be no harm in a preliminary trial of a sanatorium regime and a full course of streptomycin (0.5 g. twice daily for 60 days) controlled by repeated endometrial biopsy and culture of menstrual blood. According to the present evidence, however, the results of treatment with antibiotics of chronic infection in these sites are uncertain, and the best use of streptomycin is as a "cover" for operation, to minimize the risk of miliary spread. After operation prolonged convalescence is important.

Another line of treatment is by deep *x* rays, and good results have been claimed. However, it is not the ideal as a primary treatment, and if there is a collection of caseous material in the tube, or if secondary infection is present, an exacerbation of the salpingitis may result. Some rise in temperature after treatment nearly always occurs and prolonged rest in bed is necessary. Some women do remain in apparently perfect general health for years despite genital tuberculosis, but to adopt a *laissez-faire* attitude involves risk of spread of the disease. In reaching a decision it can be assumed that, irrespective of the type of treatment and its result, sterility is almost inevitable because of tubal damage. This is one of the strong arguments in favour of radical surgery in a case of this kind.

Marriage should be deferred until the disease is eradicated or healed. Although the risk of infecting the husband is a small one, coitus may activate and spread the pelvic lesion, and the responsibilities of marriage would make it more difficult for the woman to undergo adequate treatment. In any case the prospective partners should be made to realize that they cannot expect to have children, and it might also be wise to point out that adoption societies usually insist that applicants for children shall be certified free from tuberculosis.

Allergy to Milk

Q.—*What diet should be advised for an adult patient suspected of being allergic to milk?*

A.—A suggested diet is: *Breakfast*:—choice of grapefruit, fish, bacon, egg, toast or bread, margarine, marmalade or jam, tea or coffee made without milk, fruit drinks. *Lunch, Dinner, or Supper*:—choice of clear soup, bread, meat, fish, vegetables (other than creamed potato), gravy, fruit or salads, margarine, Roquefort cheese (from sheep's milk). *Tea*:—choice of bread, margarine, pastry, egg, drinks as above.

Milk-sensitive patients should avoid: chocolate, cocoa, coffee or tea made with milk; sweets made with milk and milk chocolate; ice-cream; special breads made with milk; cake made with milk; salad dressing and sauces made with milk; milk or cream soups; cheese; macaroni; spaghetti; blancmange; malted milks; omelette or scrambled egg made with milk; margarine made with milk. No foods should be taken which have been cooked in milk or butter. So far as possible all meals should be taken at home and special care taken when eating away from home.

In practice, sensitivity to milk means sensitivity to cow's milk, and this is rarely accompanied by sensitivity to the milk of other animals. Goat's milk, if available, is a good substitute for cow's milk. Some patients with a mild degree of sensitivity to cow's milk are able to tolerate small quantities of dried or well-boiled milk, but these are best added to the diet gradually after the sensitivity has been first proved by preliminary complete elimination of milk.

Coronary Disease in Diabetics

Q.—*I have heard one cardiologist maintain that insulin given to diabetics with coronary artery disease often aggravates the latter, so that angina of effort becomes more easily provoked. Is this view widely held, and if so could I have some references?*

A.—Patients with coronary disease seem to develop anginal pains more easily when the blood sugar is on the low side. It has been shown that a change occurs in the E.C.G. after insulin has been given. There is a decrease in the amplitude of the upright T waves in all leads. If the blood sugar has been low, the giving of sugar reverses these changes, but insulin may cause a change in the E.C.G. even when the blood sugar is not low, and this persists in spite of the giving of sugar. If, therefore, a patient has the symptoms of angina of effort, the dose of insulin must be reduced sufficiently to allow a mild glycosuria after the midday meal. The dose must be controlled by blood-sugar estimations and the patient's health must not be allowed to suffer from the lack of control of the diabetes. The following are useful references: Liebow, I. M., and Hellerstein, H. K. (1949), *Amer. J. Med.*, **7**, 660; Turner, K. B. (1930), *Amer. Heart J.*, **5**, 671; and Soskin, S., Katz, L. N., Strouse, S., and Rubinfield, S. H. (1933), *Arch. intern. Med.*, **51**, 122.

Refined and Concentrated Antitoxins

Q.—*To what extent has the refined (enzyme-treated-disaggregated) antitoxin replaced the former ammonium-sulphate-precipitated concentrated antitoxin which was in universal use about 12 years ago? What are the relative chances of severe serum reactions after injecting these two types of antitoxin? Are the figures based on published papers and records from large numbers of patients? Are there on record any details of true anaphylactic deaths caused by refined antitoxin; if so, where are they published?*

A.—The "refined," meaning the enzyme-digested, antitoxins for use in diphtheria, scarlet fever, tetanus, etc., have completely superseded the ammonium-sulphate-precipitated "concentrated" antitoxins in this country. The risk of serum sickness after an injection of antiserum depends partly on the amount of foreign serum injected and partly on the extent and nature of refinement of the antiserum. Thus, an injection of natural unconcentrated antitoxin in doses up to 100 ml. was followed by serum sickness in practically 100% of cases. With the smaller dose of around 10 ml. of concentrated serum the incidence was reduced to 10 to 20% and with the still smaller dosage of refined antitoxin the incidence is now probably less than 3%. Besides the smaller total dose of foreign protein the globulin molecule of the refined antitoxin is reduced in size and this factor may also help to reduce the liability to serum sickness. The figures quoted for the incidence of serum sickness with different types of antitoxin are mostly derived from unpublished data collected in fever hospitals. The subject is discussed in a practical way in *Bacterial and Virus Diseases* by H. J. Parish. Refined antitoxin is still a foreign protein and is just as likely to produce acute anaphylactic shock and death in naturally allergic patients as was the less concentrated antiserum. Such cases are very rare at any time and are not often recorded in the medical literature, but death from acute anaphylactic shock has occurred with refined antitoxin.

Management of Diverticulosis

Q.—*In the case of a male patient, aged 65, with diverticulosis, what is the safest purgative to give? Liquid paraffin after meals, even in large doses, is insufficient to keep the bowels open without an occasional purgative. Since he rarely goes 48 hours without some spasmodic pain, should belladonna and hyoscyamus be kept up continuously, or only when pains appear? What articles, entering into a normal day's diet, are at least harmless as regards roughage and flatulence? Are farinaceous milk puddings, toast, and biscuits in amounts usually taken by healthy adults unsuitable in these cases? Are jams containing small seeds harmful?*

A.—Any purgative is certain to increase the abdominal pain which the questioner mentions, for it can act only by increasing peristalsis. It is better to continue with liquid paraffin and make use of the glycerin suppository if the bowel habit becomes irregular. If this is not effective, a simple saline enema should be given. It is wise to prescribe antispasmodics regularly if pain occurs at all frequently, as in this particular case. In respect to diet, it is usually sufficient to avoid green vegetables and salads, cooked and raw fruit, and jams containing pips or seeds. Intestinal flatulence is commonly of carbohydrate origin and due to bread and potatoes. It can usually be controlled by reducing the quantity of these foods, substituting for them thin toast and some of the proprietary biscuits, and taking a charcoal preparation. The unsuitability of any particular food in any particular patient can be determined in the last instance only by trial and error.

Serum Sensitivity and Anaphylaxis

Q.—*The first dose of a foreign protein does not usually produce a specific bodily reaction. A second injection given more than 10 days after the first may yield an anaphylactic reaction, whereas, should this second dose be given less than 10 days after the first, anaphylaxis does not occur. (a) In the latter case, will a third injection given more than 10 days after the second injection produce an anaphylactic reaction? (b) If not, could not a routine second injection of the animal serum (tetanus, diphtheria, etc.) be given five days after every first serum injection, so that the patient is freed from the danger of anaphylaxis? (c) Otherwise what methods are available to prevent anaphylaxis?*

A.—The first injection of a foreign protein may or may not be followed by a reaction. If horse serum even in small quantities is injected into an allergic subject who is spontaneously sensitive to horse hair, and consequently horse serum, the initial injection is likely to be followed by an immediate severe and possibly fatal reaction. Also, if large quantities of horse serum are injected for the first time into either allergic or non-allergic persons, a proportion will develop typical symptoms of serum sickness in 8 to 12 days' time. There is no evidence that an alteration in the timing of the injections, as is suggested in this question, will prevent the development of a state of sensitivity. Immunization against tetanus and diphtheria in allergic persons is best carried out by giving injections of diphtheria and tetanus toxoids. The risks of sensitivity to serum are thus avoided. The management of a potentially horse-serum-sensitive patient was described in the answer to a question published in the *Journal* of July 2, 1949 (p. 39).

Toxins in Tuberculosis

Q.—*What are the modern views on the toxins of the tubercle bacillus? Do they exist and are they important?*

A.—Experimental work has failed to demonstrate that the tubercle bacillus produces either exotoxins or endotoxins. In the initial infection, before hypersensitivity has developed, the normal tissue cells live and grow without hindrance in the presence of large numbers of tubercle bacilli. If toxins do exist, they require more delicate methods for their detection than are at present available.

Benedict's Solution

Q.—*What substance in urine, possibly a drug, turns Benedict's solution (qualitative) black but does not reduce it on boiling?*

A.—This question could be answered with accuracy only if the particular specimen of urine was available for examination; there are a variety of substances which might possibly have this effect. Some, but not all, polyphenols would do this, and they might be derived from some drug or from melanogens which might appear in the urine in the case of a melanotic sarcoma. In the latter case one would expect some slight reduction of Benedict's solution on boiling. Sulphides in the urine would also turn Benedict's solution black, but it is difficult to see how they would get into the urine unless the patient was suffering from sulphaemoglobinaemia. A black coloration might also be produced if the patient was taking a dye in some medicine. Lastly, homogentisic acid, which is excreted in alkaptonuria, a rare inborn error of metabolism, turns the urine black on standing, and if Benedict's solution had been added it would no doubt go black, too.

Mouth-wash for Cigarette Smokers

Q.—*What is the inorganic chemical which can be used as a mouth-wash and which has the effect for some time afterwards of rendering the taste of a cigarette nauseating, if not emetic?*

A.—A very weak solution of copper sulphate.

NOTES AND COMMENTS

Infant Feeding.—The Director of Public Relations, Ministry of Food, writes: In his article on infant feeding which appeared in the *British Medical Journal* on May 13 (p. 1128), Dr. Philip Evans states that "evaporated (unsweetened condensed) milk is nearly unobtainable in Britain at present." There is some misunderstanding here. There are good supplies in the shops, and for this reason evaporated milk was taken off the points rationing system on April 23 last.

Nasal Folliculitis.—Dr. GEORGE GRAHAM (London, W.1) writes: In the answer to a question on this subject (June 17, p. 1446) it is suggested that "in view of a renal glycosuria the diet should be regulated." If it has been shown by a sugar tolerance test that the patient has in fact got a renal glycosuria there is no need whatsoever to do any dieting, as the condition is harmless.

Corrections

In our review (June 3, p. 1304) of *The Parathyroid Glands and Metabolic Bone Disease*, by Fuller Albright, M.D., and Edward C. Reifenstein, M.D., the price was given as £2 4s. Owing to devaluation it is now £3 1s. 6d.

Our attention has been drawn to certain inaccuracies appearing in the report in the *Supplement* of June 3 (p. 247) of the consideration by the General Medical Council of the case of Dr. A. P. Abraham, and we are asked to publish the following corrections: First, Mr. James Johnson did not say in evidence, as was stated in our report, that Dr. Abraham had told him that he was opening a surgery in Eccles New Road and would expect to get his and his family's cards. Secondly, Mrs. Glencross in cross-examination said that she never saw Dr. Abraham again after the occasion when he had offered her a lift in his car. Thirdly, the meetings referred to by Mr. James Dixon were alleged to have taken place in early September, 1949.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 2111. TELEGRAMS: *Aetiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

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